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Congenital Isolated Ventricular
Septal Defect in Children
and Infants Especially
Under 2 Years of Age

With a Follow-Up Investigation

by

Erik Terslev



FADLs FORLAG
KØBENHAVN · ÅRHUS · ODENSE
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Denne afhandling er af det natur- og lægevidenskabelige
fakultetsråd ved Odense Universitet antaget til offentligt
at forsvares for den medicinske doktorgrad.

Odense Universitet, den 21. marts 1973

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To Vivi, Lene and Rikke.



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Preface

During my appointment at Queen Louise's Children's Hospital, now closed down, my interest in pediatric cardiology was aroused by the many children with heart disease who were hospitalized there, and who were being investigated in the cardiological laboratory of the hospital. At the end of 1960, the late Professor dr. med. O. Andersen encouraged me to take up the topic of the present study, and subsequently followed the work with great interest and support, which I recall with gratitude. Ib Boesen, M.D., the permanent cardiological consultant to the hospital and head of the cardiological laboratory, has likewise given me considerable support both by cardiological tuition in general and by advice on the special problems associated with the heart disease under consideration, for which I extend my thanks. The permanent radiological consultant to the hospital, Physician-in-Chief, dr. med. Th. Rosendal has helped me greatly in the evaluation of the radiological problems, and also to him I would like to extend my thanks here.

After I started the investigation, many other colleagues have helped during the preparation of the material and its completion. I am indebted in particular to Professor, dr. med. P. Plum, the Pediatric Department, the Rigshospital, Copenhagen, Professor, dr. med. J. Lind, the Pediatric Department, the Karolinska Sjukhuset, Stockholm, Professor, dr. med. J. C. Melchior, the Pediatric Department, the Gentofte Amtssygehus, Professor, dr. med. F. Therkelsen, the Department of Thoracic Surgery, the Rigshospital, and the head of the Fuglebakken Children's Hospital, Copenhagen, Professor, dr. med. H. Andersen, for their confidence in the value of the investigation and for their stimulating assistance to carry it through.

I am indebted to the cardiological laboratory, the Kommunehospital, Aarhus, for the loan of case record information on one of the patients in the material. I am grateful to Professor K. Tryggvason, Reykjavik, for assistance in following-up some of the Icelandic children in the material. My

colleagues in Denmark and Greenland are asked to accept my sincere thanks for the information they have made available to me on the children in the material.

With regard to the practical work, my cordial thanks go above all to Miss B. Hedge, former X-ray nurse in Queen Louise's Children's Hospital. As well as helping with the protracted work of following-up the patients, Miss Hedge has helped me secretariially in many ways during the collection of the material. In the final stage, the work of making a clean copy of the manuscript was carried out with great thoroughness and care by Miss Bodil Maegaard, medical secretary, whom I also wish to thank here.

Economic support for collecting and analyzing the material, and for the follow-up examinations, was received from the "Statens almindelige Videnskabsfond", while "Det lægevidenskabelige Forskningsråd" made a considerable grant towards the cost of translation; I am greatly indebted to both organizations.

Department II of the University Library is thanked for the great help I have always received there. Finally, I would like to have the opportunity of thanking the patients in the material and their parents, for the willingness with which they attended the follow-up examinations.

The study was submitted to the University of Odense in December 1971.

Erik Terslev

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Chapter I

Aim of the present investigation

The aims of the present study have been:

1. To provide a detailed review of the disease picture "isolated ventricular septal defect" (isolated VSD), verified either by the use of cardiac catheterization alone, possibly along with right-sided angiocardiology, or in addition to this by thoracotomy and/or autopsy, in a group of children who for the most part were under 2 years of age when they were examined for the first time by cardiac catheterization. The value of this material should lie not only in the great preponderance of quite small infants, but also in the uniform procedure of investigation underlying the original examination, as the same cardiologically trained pediatrician (Ib Boesen, M.D.) examined all the children clinically, electrocardiographically, and by cardiac catheterization, if required also by angiocardiology, while the same radiologist (Physician-in-Chief, dr. med. Th. Rosendal) likewise examined them roentgenologically and angiocardialographically.

2. To examine whether it was possible from the case histories to collect a combination of anamnestic information and clinical, electrocardiographic and roentgenological data which, without the use of cardiac catheterization and angiocardiology, would make it possible to separate out from all the children with isolated VSD, that group of children whose chance of surviving the first years of life, in the strictest sense the first months of life, was so small in spite of relevant medical treatment that a palliative operative treatment in the form of pulmonary artery constriction might be worth discussing, as long as the radical operation in this age group carried a very great mortality. Should the above procedure not prove possible, the aim was then to determine whether, using the results of known cardiac catheterizations (and possibly angiocardio-

graphy), this particularly exposed group of children could be separated from the other children, and given a specially intense medical treatment, possibly followed by a palliative operation if the medical treatment was found inadequate.

3. On the basis of the follow-up examinations of those surviving children who had received surgical treatment and those who had not received surgical treatment, to examine whether it was possible, by a comparison with the results of the first examination of these patients, to decide whether those children who had undergone the palliative operation could be considered to have benefited from it (bearing in mind the rather high operative mortality).

Terminology used in this study

In the present study, "isolated ventricular septal defect" (isolated VSD) is defined as a congenital defect in the interventricular septum of the heart without other hemodynamically important pathological conditions in or at the heart, but with part of the interventricular septum retained, so that the concept "single ventricle" has not been included.

In the present study, the expression "the first cardiological examination" is used to designate the first investigation in which catheterization and possibly angiocardiology confirmed the diagnosis "isolated VSD".

Chapter II

Author's material and review of the literature

This study was started in November 1960. It comprises all those children who after catheterization and possibly angiocardiology at the Cardiological Laboratory of Queen Louise's Children's Hospital, from the time the laboratory was started in August 1954 up to 31/12-1963, were diagnosed as having isolated VSD, and in whom this diagnosis was not refuted subsequently by operation and/or at autopsy. Patients in whom the diagnosis of isolated VSD was made on exclusively clinical grounds have thus not been included.

In the period in question, a total of 884 children were examined, 716 of them under 2 years of age at the time of the examination. A total of 31 - all under 2 years of age at the time of the examination - had no heart disease according to the results of the examination. Out of the 853 children in whom heart disease was demonstrated, a total of 144 had isolated VSD.

The patient numbering used in the study is the catheterization number, so that in the case of the patients with isolated VSD the numbers are not in sequence.

Of the total of 144 patients with isolated VSD, 124 were examined for the first time when they were under 2 years of age. 97 of the total of 144 patients were examined for the first time before 31/12-1960, while the remainder, 47, were examined during the period 1961-1963. Of the 97 patients mentioned, all but one of the 76 survivors underwent a follow-up examination.

This took place before the end of 1963, with the exception of 1 case, in whom the follow-up examination could not be carried out before May 1964. One patient, an Icelandic girl, could not be contacted in spite of repeated applications, and she is thus the sole non-followed-up patient of the 76 survivors. Of the 75 patients, 3 had their follow-up examination carried out by Physician-in-Chief

dr. Tryggvason, Reykjavik, and one, resident in Greenland, by the nearest district physician; one was followed-up by the Cardiological Laboratory, Kommunehospitalet, Aarhus (where the patient had been sent for continued control), and one was followed-up in the Pediatric Out-patient Department of the Rigshospital, Copenhagen. The remaining 69 patients were all followed-up by the author, either as out-patients or during an admission to Queen Louise's Children's Hospital (or in a single case to the Pediatric Department of Sundby Hospital).

The 47 patients who had their first examination during the period 1/1-1961 to 31/12-1963 did not undergo a follow-up examination, but are included in order to make the material from the first examination more extensive than originally planned.

Finally, it should be added that the data on the patients have been brought up to date to the end of 1963 and terminate then (with the exception of the information on the one patient mentioned above, who was not given a follow-up examination until May 1964).

In reviewing the present material, the emphasis will be on the proportion of the children who were under the age of 2 years at the first cardiological examination, as numerous studies in recent years have made it clear that this is the period of life in which the greatest changes take place to patients with isolated VSD, and one which is critical for them, especially in patients with large ventricular septal defects (for literature and references see: Nadas 1967, Sigmann et al. 1967).

Incidence

In Denmark, no reliable evaluation of the incidence of isolated VSD is possible on account of the circumstances of referral.

In the present material, the incidence of isolated VSD among other congenital heart diseases, calculated for the entire material of 144 children, is 16.9% (144 out of 853 patients). Calculated only for the infants under the age of 2 years, it is 18.1% (124 out of 685 patients).

With regard to the incidence of isolated VSD, it is difficult to find comparable series in the literature, depending on the criteria on which the patients have been chosen in the various series. The most important among these are:

Abbott (1936 b): 5.5% of an autopsy material of 1000 patients (where it is not possible to separate the children into the various groups).

P. Wood (1950): 12% of 200 patients who underwent clinical examination (152 of whom underwent cardiac catheterization), but the age of the children has not been given.

- Kjellberg et al. (1955): 16% of 342 selected cases of congenital heart disease (mainly accessible to surgery), without any indication of the age, but mainly children.
- Ober and Moore (1955): 6 out of an autopsy material of 100 cases of newborn infants dying of congenital heart disease.
- Boesen and Vendel (1955): 12.9% of an autopsy material of 1145 infants with heart disease, dying before the age of 4 years.
- Gasul and Fell (1956): 22.3% of 1395 patients with congenital heart disease, in whom the majority of diagnoses were made clinically, but 300 of whom came to autopsy.
No age distribution is given, but more than 90% of the patients were under 16 years of age.
- Nadas (1957): 10.1% of a material of 577 patients with congenital heart disease, mainly children, diagnosed either by catheterization, on operation, or at autopsy.
- Keith et al. (1958): 22%.
- Rowe and Cleary (1960): 7% of an autopsy material of 106 newborn infants, dying within the first 28 days of life, but 20% of 81 infants who survived the first 28 days of life.
- Eliot et al. (1966): 23.3% of a total of 1448 infants under the age of 1 year with congenital heart disease.
- Storstein and Sörland (1966): 20.4% of a material of 1000 patients with congenital heart disease.

The percentage value found in the present study for the incidence of the disease state isolated VSD among cases of congenital heart disease (18.1% for children under 2 years of age), is presumably as near to the correct value as possible. It is obvious that among undiagnosed cases of congenital heart disease resulting in death in the course of the first few weeks of life, there are cases of isolated VSD in its most severe form, but the same presumably holds for other forms of congenital heart disease such as inadequate development of the left side of the heart, transposition of the great vessels and the severely complicated congenital heart diseases. On the other hand, there will presumably also be a few quite slight cases of isolated VSD which are not diagnosed until after the age of 11 years, which is the age of the oldest patient in the material, but this must also be the case for other mild forms of congenital heart disease (small PDA, small ASD, weakly pronounced Fallot's tetralogy, weakly pronounced isolated PS etc.).

Etiology

It is most often impossible to clarify the etiological factors in the individual cases of isolated VSD, but hereditary factors as well as special circumstances of the intrauterine environment presumably play a part.

Familial disposition: In the present study, a congenital heart disease was found in the families of 10 out of the 82 girls for whom information was available on familial disposition (12.2%). In one of these families, congenital heart disease was found in both the father and the sister. In 6 out of 59 boys for whom information was available on familial disposition, congenital heart disease was found in the family (10.2%), in 3 of these cases among siblings or parents. In one case, the congenital heart disease was found in 2 siblings. Altogether information was available on familial disposition in 141 of the 144 patients in the material, and familial occurrence was found in 11.3%, in 3 cases (2.1%) in siblings, in 5 cases (3.6%) in the parents.

Information on the type of heart disease from which the closely-related family member had suffered was available in only 3 cases. In one case, the mother of one of the patients had a congenital pulmonary stenosis, while the other 2 cases were two siblings, both included in the present material with isolated VSD, but who had also had a younger brother who had died of a congenital heart disease, type not known.

In addition to the 14 cases mentioned in the material, where information is available on congenital heart disease in the family, the other patients provided information on other congenital anomalies: diabetes mellitus in a mother, strabismus + hypermetropia in 2 siblings, and oligophrenia in both parents + epilepsy in the father.

The literature contains a number of studies which support the view that familial occurrence of congenital heart disease is increased in patients with this anomaly. On the one hand the percentage occurrence is increased in siblings, varying from 0.6% (Nadas 1957), 0.8% (Keith et al. 1958), 1.5% (Lamy et al. 1957), 1.7% (Campbell and Goodwin 1964) and 1.8% (McKeown et al. 1953), to 2% (Polani and Campbell 1954-1955), by comparison with the expected incidence in the population: 0.3% (McKeown et al. 1953), while on the other hand a number of single cases have been reported (Tucker and Kinney 1945, Zimmerman et al. 1953-54) as well as major studies (Campbell 1949, Lamy and Schweisguth 1950, Carleton et al. 1958) where the familial occurrence of congenital heart disease was more frequent than expected. Campbell (1949) gives an incidence up to 7%, Lamy and Schweisguth (1950) to 8%.

Foxon (1959) states that it is the earliest phases in the development of the heart which are genetically controlled, but that mechanical factors (blood flow

etc.) influence the subsequent development. He suggests that VSD may be caused either by genetic factors or by uterine environmental factors.

McKusick (1964), Campbell (1965), Nora (1968) and Emanuel (1970) all state that the genetic component in cardiovascular diseases of congenital origin appears to be complex; the same is the case, however, for the uterine environmental factors, so that these conditions taken together become multiple in the true sense, and it is rare that congenital cardiac anomalies are due to a single one of the conditions mentioned.

Finally, it might be mentioned that Lamy et al. (1957) point out the significance of genetic factors for the individual types of congenital heart disease, and that in isolated VSD, the non-genetic factors play the greatest role. Sandøe (1963) states that genetic factors do not seem to play any great role in his investigation.

No chromosome studies have been made in the present material.

The significance of exogenous and endogenous factors in the first trimester of pregnancy (infections and other complications during pregnancy.)

In the present material, complications were recorded in 11.6% of the cases, among the 138 out of the 144 patients for whom information on possible complications of pregnancy was available.

In 12 of the 80 girls for whom information was available on possible complications of pregnancy, the following noticeable maternal complications were described: 1 case of myxoedema, 2 cases of oedema, 2 cases of hyperemesis, 1 case of hypertension + toxemia, together with 6 cases of hemorrhage - not specified in detail - during the first months of pregnancy; 15%. Out of 58 boys for whom there was information of possible complication during pregnancy, there were in 4 cases the following noteworthy maternal complications: 1 case of premature separation of the placenta, 1 case of general fatigue during the whole of pregnancy + bleeding both early and late in pregnancy, one case of virus infection - not specified - during the 3rd month of pregnancy and 1 case of albuminuria - stage during pregnancy not stated; 6.9%.

There was thus only one case of infection (not specified) during the first trimester of pregnancy and 7 cases of early bleeding, which must be of special interest in the present material, when it is known that the development of the heart - during which period its susceptibility to harmful influence is greatest - is completed latest in the 3rd month of pregnancy.

No case of rubella has been demonstrated with certainty in the material, which does not contradict the reports in the literature.

It is particularly the problems of the significance of infections early in pregnancy that have been discussed by numerous authors in the literature, especially in the case of rubella (for literature and references, see Kjellberg et al. 1955, Landtman 1965, Way 1967).

The figures for rubella during the first trimester of pregnancy, as responsible for congenital cardiac anomalies, have been of an order of magnitude of 0-5%: Domagraci and Green (1947): 1%, Miller (1948): 5%, Campbell (1949): 1.3%, Gibson and Lewis (1952): 1%, Kjellberg et al. (1955): 1.1%, Campbell (1961): 2-4%, Sandøe (1963): 0% out of 87 cases of VSD, Campbell (1965): 1-2%.

Other factors than infections which have been mentioned in the literature, although to a more limited degree, and which are of significance for congenital malformations, are abortions, stillbirths, and neonatal mortality. Stevenson et al. (1950) and Worcester et al. (1950) found a greater incidence of vomiting and toxemia in mothers giving birth to infants with congenital heart disease than among those giving birth to normal children. Navratil et al. (1955) found that hormonal disturbances in mothers played a part for the occurrence of congenital cardiac malformations. Late menarche, irregularities in menstruation, temporary sterility and a tendency to frequent spontaneous abortion were found to have a statistically greater incidence among mothers of infants with congenital cardiac defects than in a control group. Lamy et al. (1957) found that threatening abortion or premature delivery and other abnormal conditions during pregnancy were twice as frequent in a group of mothers giving birth to infants with congenital heart disease than in a control group. Polani and Campbell (1954-55), however, found no preponderance of stillbirths, premature births, abortions or other disturbances during pregnancy; the same was found by Richards et al. (1955). Campbell (1965) reports having seen a number of cardiac malformations following pregnancies where there had been severe hemorrhage or threatening abortion. On the other hand, Ehlers and Engle (1966) could demonstrate no uterine environmental factors of significance for the origin of congenital heart disease.

Age of the mother: In the present material, information on the age of the mother is available in 137 out of the 144 children; the mean maternal age at the birth of the infant was 26.2 years, with a range from 17 to 47 years. In the 80 girls for whom the age of the mother at the birth of the infant was reported, the mother was under the age of 20 years in 10 cases, and 40 years or more in 3 cases. In the 57 boys for whom the age of the mother at the birth of the infant was reported, the mother was under the age of 20 years in 4 cases, but none of them were 40 years or more. These figures correspond well to the value of

28.7 years used by Øster (1953) for normal mothers. Further support for these findings is given by Stevenson et al. (1950), Worcester et al. (1950), Polani and Campbell (1954-55), Lamy et al. (1957) and Sandøe (1963), while Richards et al. (1955) and Kaindl et al. (1965) found that the age of the mother had some significance for a tendency to the occurrence to congenital cardiac defects, as in their material the risk increased with the age of the mother. (Their material includes 4 mongols, but it is not clear whether the presence of these 4 mongols is the explanation of the increased risk of congenital cardiac defects with increasing age of the mother in the material in question). Campbell and Goodwin (1964) found that VSD occurred more frequently in primiparas over the age of 35 and in older mothers, where a longer time had elapsed since the last pregnancy, which was in part confirmed by Campbell (1965), who also found that VSD was more frequent at high birth rank in mothers over the age of 35 years.

Age of the father: In the present material, information on the age of the father at the birth of the infant was available in a total of 125 out of the 144 patients. The mean age for the 125 fathers at the birth of the child was 29.6 years. In 11 cases the father was 40 years of age or more at the birth of the child, and in one case the father was under 20 years of age. The normal material of infants born in 1 year (1959) in the Pediatric Clinic for Preventive Service of Frederiksberg Hospital has been used for comparison. The total in this year was 216 infants, but in 22 there was no information on the age of the father (in most cases because the parents were not married). In the remaining 194 infants, the age of the father at the birth of the child was on the average 29.4 years. 5 fathers were 19 years of age and 17 fathers were 40 years of age or more. The range was 19-52 years. The mean age of the father at the birth of the infant thus agrees well with that found for the present patient material. Polani and Campbell (1954-55) and Sandøe (1963) also found no relationship between the development of cardiac defects in an infant, and the age of the father. Campbell (1965), however, found that the age of the father was greater than expected if the child had VSD, expressed by the fact that the difference between the age of the mother and the father was greater than normal in the parents of infants with VSD.

Birth complications: In the present material, 3 of the 80 girls and 2 of the 60 boys for whom information was available as to conditions at birth, had had a complicated birth (girls: 2 were asphyxiated, one had had the head impacted, boys: 1 was asphyxiated, 1 had aspirated amniotic fluid), i.e. 3.6% had birth complications. If the infants from the infant clinic mentioned in the above sec-

tion "age of the father" are used as normal material for comparison, we find 8 complicated births, i.e. an incidence of 4.2%. The present material thus does not show a higher frequency of birth complications than a normal material chosen at random, although it must be added that the number of birth complications in both materials is very small. The finding that obstetrical complications show no correlation with the incidence of congenital cardiovascular defects is supported by the results in a study by Richards et al. (1955).

Birth weight: The birth weight was known in 141 out of the 144 patients in the material. Of these 141, 25 (15 girls and 10 boys) were born with a birth weight less than 2500 g, i.e. a frequency of 17.7%.

The frequency of birth weight less than 2500 g under normal circumstances is quoted by Plum et al. (1962) as 3.2 - 9% in Denmark. The high frequency of birth weight less than 2500 g in the material is supported by the findings in a comprehensive literature (for literature and references, see Campbell and Goodwin 1964, Campbell 1965, Mitchell et al. 1967).

Month of birth of the patients: The distribution of the 144 patients in the material according to the month of birth is shown in table 1 (which also shows the number of patients with other congenital defects in each patient group). It is seen that there is no accumulation of patients in definite months, which might have been expected if the first trimester of pregnancy coincided with months of high incidence of infection (the first and the last quarter of the year), and if these infections had etiological significance for the occurrence of heart disease or other congenital malformations, such as was found by Worcester et al. (1950) and Stevenson et al. (1950) in the case of congenital malformations in general, and by Landtman et al. (1965) in the case of congenital cardiac defects. Neither MacMahon (1952) nor Rutstein et al. (1952) found any seasonal accumulation of congenital heart disease; in the case of the last authors, however, the investigation was concerned solely with the occurrence of PDA. Nor did Sandøe (1963) find any seasonal accumulation of VSD.

Other congenital defects

Among the 144 patients in the material, 35 patients (16 girls and 19 boys) had other congenital defects, i.e. 24.3%.

Of the 83 girls, 16 had other congenital defects (19.3%): 4 were mongols, 1 had congenital pyloric stenosis, 1 had subluxation of the hip + pedes calcaneovalgi, 1 had cleft palate, 1 had a malformation of the urinary tract, 3 had

Table 1. Distribution of the 144 patients in the material according to month of birth. The figures in brackets indicate the number of patients with other congenital defects.

Month of birth	total	boys	girls
January	16 (5)	5 (4)	11 (1)
February	11 (3)	5 (2)	6 (1)
March	16 (3)	8 (1)	8 (2)
April	10 (4)	3 (2)	7 (2)
May	9 (1)	6 (1)	3 (0)
June	12 (2)	5 (1)	7 (1)
July	17 (7)	8 (3)	9 (4)
August	13 (1)	5 (0)	8 (1)
September	11 (3)	5 (2)	6 (1)
October	10 (1)	4 (1)	6 (0)
November	8 (3)	5 (2)	3 (1)
December	11 (2)	2 (0)	9 (2)
Total	144 (35)	61 (19)	83 (16)

Table 2. The sex and age distribution of the material, at the first cardiological examination.

Age at first examination	boys	girls
under 1 month	1	2
1 month	3	6
2 months	11	14
3 months	4	12
4 months	5	2
5 months	7	4
6 months	8	4
7 months	1	3
8 months	3	0
9 months	2	2
10 months	2	5
11 months	2	0
12 months	2	3
13 months	1	1
14 months	2	1
15 months	0	2
16 months	0	0
17 months	0	2
18 months	0	3
19 months	0	0
20 months	0	1
21 months	0	1
22 months	0	1
23 months	0	1
2 years	3	3
3 years	1	1
4 years	1	0
5 years	1	1
6 years	0	3
7 years	1	1
8 years	0	1
9 years	0	0
10 years	0	2
11 years	0	1
total	61	83
under 2 years	54	70

124 < 2 years

diseases of the integument (hernia, vitiligo, deformed ears) and 5 had neurological diseases (2 had tetraplegia spastica, 2 had hydrocephalus and 1 had epilepsy). A number had multiple defects, so that in 16 girls a total of 22 congenital defects were found apart from the heart disease.

Among the 61 boys, 19 had other congenital defects (31.1%): 1 was a mongol, 2 had congenital pyloric stenosis, 1 had a vascular ring, 1 had omphalocele + atresia ani, 4 had neurological diseases (2 oligophrenia, 1 oligophrenia + epilepsy, 1 choreoathetosis), 1 had a deformity of the spinal column, 1 had impairment of hearing, 2 had cleft palate + cleft lip, 1 had isolated cleft lip, 2 had hernia and 1 had hydrocele testis + hydronephrosis. A number of the patients had multiple defects, so that in 19 boys a total of 29 congenital defects were found in addition to the heart disease.

Other authors have previously found figures of the same order of magnitude (for literature and references see Boesen et al. 1963, Okada et al. 1968).

Boesen et al. (1963) found that VSD was more frequently combined with malformations of the bones, joints and lungs, and Okada et al. (1968) found that VSD was most frequently combined with anomalies in the position of the abdominal viscera and with diseases of the urinary tract and diseases of the extremities.

A special study was made by Melchior and Terslev (1964) for diseases of the central nervous system (neurological and mental diseases) in a material of 615 children with congenital heart diseases, 146 of whom had isolated VSD, and 11 of whom were mongols. In addition to the mongolism, mental retardation was found in 24 children out of the 615, 4 of these 24 having isolated VSD, so that 2.7% of the patients with isolated VSD had mental retardation in addition to the mongolism. No special relationship was found between definite heart diseases and mental retardation, and this was the same in cyanotic and non-cyanotic children. Epilepsy was found in 23 children; 3 of them had isolated VSD, i.e. 2.1% of the patients with isolated VSD had epilepsy. 24 children had cerebral palsy, and 7 of these had isolated VSD, i.e. 4.8% of the patients with isolated VSD had cerebral palsy. For further details see the follow-up on page 000.

The incidence of mongolism in the present material is 3.5%. According to Øster (1953), the incidence of mongolism in a normal population is 0.161%.

In the case of the 16 girls with other congenital defects, the accompanying defects may have contributed to failure to thrive in 11 of them (patient numbers 207, 297, 467, 479, 561, 564, 597, 618, 690, 794 and 864). The same may have been the case in 12 of the 19 boys (patient numbers: 49, 58, 189, 238, 277, 379, 547, 641, 719, 759 and 789).

Sex and age distribution

The sex and age distribution of the material at the first cardiological examination is shown in table 2. The difference between boys and girls is not significant ($p > 0.05$), either for the whole material of 144 children or for the material under the age of 2 years (124 infants), which is also the case for most of the material reported in the literature on isolated VSD (for literature and references see Bloomfield 1964, Schrire et al. 1965). A few authors have found more male than female subjects (Schaefer et al. 1960: 62.2% male subjects, Campbell 1965: about 60% male subjects).

The preponderance of females found in the present study, admittedly not significant, corresponds almost exactly to that found by Sandøe (1963).

Of the 144 children, 124 had their first cardiological examination before the age of 2 years, 103 (72% of the total material) before the age of 12 months and 71 (49% of the total material) before the age of 6 months. The great preponderance of quite small infants with isolated VSD (age at first cardiological examination) should provide a good opportunity for elucidating the development of the disease in all its phases.

Deaths in the material

Of the total of 144 patients in the material, 14 boys and 13 girls had died when the material was finally updated at the end of 1963 (one follow-up took place in 1964).

The 6 dying "spontaneously" all had pulmonary hypertension, and 4 of them presumably had equalization of pressure between the ventricles. The hemodynamic conditions at the first cardiological examination (pressure = systolic pressure in mm Hg in the RV or PA, shunt = left-to-right shunt expressed by the oxygen saturation deficit RV to RA in %) were as follows: no. 4: 59 mm Hg/9%, no. 262: 76 mm Hg/25%, no. 297: 80 mm Hg/10%, no. 379: 59 mm Hg/37%, no. 462: 71 mm Hg/9%, no. 467: 65 mm Hg/6%. However, the fact that the mortality is high in the age group to which the main part of the present material belongs (age under 2 years at the time of the first cardiological examination) is confirmed in the literature; all authors report that the highest mortality for the disease "isolated VSD" is in the first 2 years of life (for literature and references, see Kaplan et al. 1963, Ash 1964). Boesen (1965) reports that in 66 newborn with isolated VSD who were not operated on and who had a period of observation longer than the first 2 years of life, 71% survived the first 24 months of life. If this material of 66 infants with isolated VSD is grouped according to

the pressure in RV or PA, then all survived the first years of life if the pressure was ≤ 40 mm Hg; with a pressure of 41-60 mm Hg, 89% survived and with a pressure ≥ 61 mm Hg, 63% survived the age of 2 years.

The causes of death in the case of the 6 "spontaneous" deaths in the present material (3 girls and 3 boys) were: cardiac failure alone: 2, cardiac failure + pneumonia: 3, and cardiac failure + acute gastroenteritis: 1.

The cause of death in infancy is reported by a large number of authors as being either cardiac failure (failure of the LV) or pneumonia (for literature and references see Kaplan et al. 1963, Ash 1964). A few authors emphasize that also intercurrent diseases are frequent causes of death during the first years of life (Marquis 1950, Ash 1964).

Chapter III

Clinical picture at first cardiological examination

Introduction

By far the greater part of the patients in the material were admitted to Queen Louise's Children's Hospital with the direct intention of determining their heart disease; it was only in a minority of cases that the heart disease was discovered by accident during hospitalization for some other disease.

In all patients, the history was made as complete as possible. The roentgen examination of the thorax was then made in 4 planes with contrast in the oesophagus, and an ECG with 12 leads (3 extremity leads, 3 aV leads and 6 precordial leads: V_{1-6}), and when these results were available, all patients, after being examined initially by the permanent medical staff of the hospital, were examined by the same cardilogically-trained pediatrician (Ib Boesen, M.D.), who then made a temporary diagnosis on the basis of the clinical examination, the radiological examination of the thorax and the ECG, and referred the patient for further examination by means of cardiac catheterization, and, possibly, angiocardiology. After this, a final diagnosis was made, and any necessary treatment initiated.

The present study has followed the current view, that the condition isolated VSD comprises all symptom complexes from the mildest form, corresponding to the designation "Maladie de Roger", to the most severe form, corresponding to the designation "Eisenmenger's complex" (for literature and references see Maranhao et al. 1965). As a result, the disease picture is extremely varied, as all grades of disease from the mildest to the most severe have been represented in this study.

On account of technical difficulties, no measurement of oxygen uptake in the

lungs was made in the present material, and only in a few cases has a measurement been made of the oxygen saturation in the greater circulation. It has therefore not been possible to calculate the magnitude of the systemic flow, and in consequence not possible to calculate the vascular resistance in the pulmonary circulation. Nor has it been possible to calculate the flow ratio (Sandøe 1963).

The study has been established on the working hypothesis that the condition of the patient depends in particular on the magnitude of the pressure in the RV or PA and on the magnitude of the left-to-right shunt (in particular the first factor), and the individual symptoms and conditions which are reviewed have therefore been evaluated on the basis of these two parameters: the magnitude of the pressure in the RV or PA in mm Hg and the magnitude of the left-to-right shunt through the ventricular septal defect, expressed as a deficit of oxygen saturation from RV to RA in per cent, measured by means of cardiac catheterization. It should be mentioned, first, that there is some uncertainty in the catheterization measurements in a material of such small infants as the present, and secondly, and in particular, that the details for the shunts might have been more precisely expressed (in magnitude of pulmonary flow in relation to the magnitude of the systemic flow), but that the oxygen saturation values measured do not permit this. In patients with a pressure equalization between the RV and the LV (here put $\bar{S}$ 61 mm Hg pressure in RV), it was considered that some expression for the pulmonary vascular resistance could be obtained by assuming that the degree of severity of this was inversely proportional to the magnitude of the left-to-right shunt, and 3 groups of cases have been set up with pressure equalization between RV and LV: one group with a high pulmonary vascular resistance (small left-to-right shunt), one group with a low pulmonary vascular resistance (large left-to-right shunt), and one in-between group, with a moderately severe pulmonary vascular resistance and a moderately large left-to-right shunt (cf. Dammann et al. 1960 and Lucas et al. 1961).

Review of the literature on the clinical picture of isolated ventricular septal defect

Neither the symptomatology in the condition isolated ventricular septal defect, nor the degree of severity of the symptoms, is determined by a single factor, but by means of a complex of factors, which taken together decide whether the balance between the pulmonary blood flow and the systemic blood flow is maintained or is upset; these factors are the magnitude of the defect, its localiza-

tion, its size in relation to the aortic orifice, and the structure and function of the pulmonary vasculature (for literature and references see Ash 1964, Bloomfield 1964, Schrire et al. 1965, Ritter et al. 1965).

Time of onset of the disease

If when discussing the time of onset of the disease, those studies in the literature are also included which are based on purely autopsy series, and where it must be supposed that the VSD has been the actual cause of death, the conclusion is that the disease may begin immediately after birth. In the material of Boesen and Vendel, 1955, a total of 148 patients with VSD, all of whom died before the age of 4 years, 51 died before they were 30 days old; in a material of Gasul et al. 1957, a total of 342 patients with VSD, many of the 27 patients who came to autopsy before the age of 1 year had died during the course of the first weeks or months of life; in the material of Zacharioudakis et al. 1957, a total of 23 uncomplicated cases of VSD, the first deaths took place already at the age of 3 days; in a material of Mehrizi et al. 1964, an autopsy material of VSD patients, half of the patients had died before 48 hours after birth (although a number of them may have died from accompanying abnormalities), and finally in the material of Walker et al. 1965, a total of 158 patients, 59 died in the course of the first month.

In the clinical material, many authors report that the first symptoms begin before the age of 1 month (for literature and references see Kidd et al. 1965 a), while others report that the time of onset lies within the first few months of life (for literature and references see Hoffman and Rudolph 1965, Sigmann et al. 1967). As the first symptom, Nadas mentions that a murmur is often recognizable within the first 2-3 weeks of life (Nadas 1957). Fyler et al. (1958) and Dammann et al. (1960) mention as a transient symptom during the first few weeks of life that cyanosis is found in moderately large and large ventricular septal defects with cardiac failure. Hoffman and Rudolph (1965) found that half of their infants with VSD had cardiac failure before the age of 6 months, and mention that this cardiac failure commenced earlier in premature than in full-term infants.

Ability to thrive

Ability to thrive (increase in weight and length) in infancy and childhood in the case of isolated VSD is generally retarded to a higher degree the more severe

the disease (for literature and references see Ash 1964, Maranhao 1965, Feldt et al. 1969 b), and most authors find that the retardation in weight is more pronounced than the retardation in length (Campbell and Reynolds 1949, Maxwell et al. 1958, Hilger and Schaede 1960, Veasy 1960, Ash 1964, Walker et al. 1965), while Fyler et al. (1958) find that the retardation in length is proportional to the retardation in weight. Weight retardation is particularly pronounced in high pulmonary resistance (Fyler et al. 1958, Blount and Woodwark 1960, Hilger and Schaede 1960, Veasy 1960). However, it should be mentioned that Maxwell et al. (1958) and Miller et al. (1969) do not find any correlation between pressure in RV and degree of retardation of growth.

Tachypnoea at rest and on exertion

Tachypnoea at rest and on exertion is seen in children with isolated VSD with large defects (Nadas 1957, Keith et al. 1958, Blount and Woodwark 1960, Ash 1964). Most authors find the most pronounced tachypnoea at high pressure in the RV, less with large left-to-right shunt (Heath and Whitaker 1956, Hubbard et al. 1957, Neill and Taussig 1959, Schaede et al. 1960, Ritter et al. 1965), while a single group of authors associate the tachypnoea and the large left-to-right shunt together as the most important etiological factor (Derra et al. 1960). In Eisenmenger's complex (?), with normal arterial oxygen saturation, minimum to moderate tachypnoea is found, while in Eisenmenger's complex with reduced arterial oxygen saturation, moderate tachypnoea is found (Kohout et al. 1955). Merrild (1962) found severe tachypnoea in both patients with high pressure in the RV and in patients with large left-to-right shunt, and in his material he finds that in 6 patients without tachypnoea, there is an increase of 58% in the size of the heart, in 5 with slight tachypnoea there is an increase of 88% in the size of the heart, and in 8 heart patients with pronounced tachypnoea, there is an increase of 111% in the size of the heart.

Cyanosis at rest and on exertion

In quite small infants, cyanosis - possibly transient - may be seen during the first few weeks of life, in cases of isolated VSD with cardiac failure (moderate to large septal defects) (Engle 1954, Kjellberg et al. 1955, Fyler et al. 1958, Dammann et al. 1960). Walker et al. (1965) explain this quite early cyanosis present already at birth and disappearing in the course of the first year of life, as a sequel to a delayed regression of the high fetal pulmonary arterial re-

sistance. If, however, the cyanosis continues after the first few weeks or if cyanosis develops in the course of the first few months or years, this is a sign of either increasing cardiac failure (Dammann et al. 1960) or of the development of severe pulmonary hypertension with preponderant right-to-left shunt (Nadas 1957, Fyler et al. 1958, Keith et al. 1958, Dammann et al. 1960, Walker et al. 1965), and the cyanosis then increases on effort as a result of increased right-to-left shunt. Selzer and Laqueur (1951), describing the Eisenmenger complex, find that in 5 of a material of 35 patients the cyanosis commenced at birth or in infancy. Also P. Wood (1958 a), Schaede et al. (1960) and Veasy (1960) find that patients in the group with high pulmonary vascular resistance, and consequent pulmonary hypertension and preponderantly right-to-left shunt, may have had cyanosis from birth or it may have begun in early infancy.

Cardiac failure (hepatomegaly, rales, edema)

In severe cases of isolated VSD, cardiac failure is often seen during the first couple of years, specially during the first 6 months (for literature and references see Ash 1964, Hoffman and Rudolph 1965, Ritter et al. 1965), and the cardiac failure develops earlier in premature infants than in fullterm infants (Hoffman and Rudolph 1965). Morgan et al. (1960) found no hemodynamic differences between the patients who died and those who survived cardiac failure during early infancy. They also mention that exacerbation of cardiac failure after infancy is a rare event. Kaplan et al. (1963), like other investigators, found a high incidence of cardiac failure under 2 years of age (15.2%), and that the percentage of cases with cardiac failure in their material increased with pressure in the PA, from 3% at a pressure of 30-40 mm Hg to 38% at a pressure of > 65 mm Hg. Ritter et al. (1965), in their material of 78 patients under the age of 2 years with cardiac failure, had 53 in whom the failure had developed during the period 6 weeks to 6 months of age, and among these there were 3 patients with Roger's type of isolated VSD. The cause of death was failure of the LV,

Reduced endurance in feeding

Reduced endurance in feeding is a common symptom in isolated VSD, particularly pronounced in high pressure in the RV or PA and most pronounced in pressure equalization between RV and LV + a small left-to-right shunt or a preponderant-

ly right-to-left shunt. In normal pressure in the RV or PA, the endurance is most reduced in the case of a large left-to-right flow (for literature and references see Ritter et al. 1965).

Recurrent respiratory tract infections

Recurrent respiratory tract infections in the form of bronchitis and pneumonia often followed by death threaten at all times, particularly in severe cases of isolated VSD in infancy (for literature and references see Ash 1964).

Complications apart from respiratory tract infections

Heart block: In 1936, Abbott (1936 a) mentioned that partial heart block could be found in isolated VSD. Brown (1950) concludes after a thorough review of the literature that congenital heart block usually occurs at random in isolated VSD, and not as a sequel to the disease. Edwards (1960) mentions that complete heart block in isolated VSD can be caused by VSD, or be an accompanying anomaly.

Endocarditis: (with localization along the edge of the VSD or opposite the VSD on the wall of the RV (Abbott 1936 a and 1937)) may occur in isolated VSD in infants, but the incidence increases with age, and the disease is uncommon under the age of 2 years, either for the acute bacterial form or the subacute bacterial form (for literature and references see Ritter et al. 1965). Downing and Goldberg (1956) found no case whatever of endocarditis among their mixed infant and adult material, and Keith et al. (1958), Kaplan et al. (1961) and Kaplan et al. (1963) all found a frequency of 1% or less in their series.

Deformity of the thorax: Deformed or asymmetric thorax is a frequent complication in isolated VSD, especially in patients with large left-to-right shunts (left-sided prominence of the thorax) (Fyler et al. 1958).

Anemia: Maxwell et al. (1958) found that anemia was not uncommon in isolated VSD. It appears to be a sideropenic anemia; however, the frequent infections increase the anemia and the need for iron. Schaede et al. (1960) found that half of their 120 patients had normal Hb%. There was an increased Hb% in 49 patients, most pronounced in pulmonary hypertension and equalization of pressure be-

tween RV and LV. Anemia was found in 14 patients, distributed uniformly over the various degrees of severity of the isolated VSD.

Rapid heart action: Downing and Goldberg (1956) described cases of rapid heart action in 8% (6% of these were reported to be of the type paroxysmal tachycardia). Fyler et al. (1958) described paroxysmal tachycardia in 5 of their patients. Ritter et al. (1965) described "palpitations" in 2 patients in their material.

Voussure: This is seen to an increasing degree, the greater the left-to-right shunt, and the stronger the pulmonary hypertension, either as a left-sided or as a bilateral precordial bulge, possibly with left-sided preponderance. When the isolated VSD has reached the stage of the Eisenmenger complex, voussure is also seen, now on account of the preponderant right-sided ventricular hypertrophy, but the cardiac activity is less violent in Eisenmenger's complex (for literature and references see Ash 1964). Keith et al. (1958) and Dammann et al. (1960) only find voussure in hypertension with enlargement of the RV. Merrild (1962) found considerably greater enlargement of the heart in the presence of voussure than in its absence.

Thrill: The frequency of thrill, taking into account the hemodynamic conditions, is reported as very variable by the different authors, but generally it may be said that the presence of thrill supports the diagnosis of isolated VSD.

In small defects with normal pressure in the RV and a small left-to-right shunt (= Roger's disease), thrill is reported to be present in very varying percentages. The one extreme of the incidence is reported by Mannheimier et al. (1957) and Schaede et al. (1960), who never or only rarely find thrill, and on the other hand by Roger (1879), Neill and Taussig (1959) and Veasy (1960), who almost always find thrill. The considerable variation in the reports of the incidence suggests a difference in the criteria for selection, but it may also play a part that thrill need not be recognized before several months after birth (Maxwell et al. 1958).

In isolated VSD with normal or slightly elevated pressure in the RV and moderate left-to-right shunt, it is generally agreed that there is almost always thrill (for literature and references see Maranhao et al. 1965).

In isolated VSD with a large left-to-right shunt and hypertension without pressure equalization between RV and LV, and in isolated VSD with pressure equalization between RV and LV, but with the left-to-right shunt maintained, thrill is present.

In Eisenmenger's complex, it is doubtful whether thrill is present.

The systolic murmur: The systolic murmur in isolated VSD develops in almost all cases in the course of the first 2-3 weeks of life (Nadas 1957).

The typical systolic murmur is a strong, high frequency, harsh murmur which can be heard along the whole of the left sternal border from the 2nd to the 5th intercostal space and over the xiphoid process, in most cases with a maximum lying in the 3rd-4th left intercostal space. The strength varies from strength 2 to strength 5 (out of 6 possibles (Levine 1961)), most often strength 3 or more with a tendency to be distributed throughout the whole systole at low pressure in PA and to be shorter and shorter and at the same time more low frequency with increasing pulmonary pressure, while at the same time its intensity decreases (the murmur possibly disappearing completely). When it is present throughout the entire systole, it is either equally strong through this period (phonocardiographically plateau-shaped) or crescendo-decrescendo (phonocardiographically "diamond shaped") (for literature and references see Ash 1964, Maranhao et al. 1965). The localization may vary. Dammann et al. (1960) report that a murmur which is strongest at the base may give a suspicion of obstruction in the outflow tract of the RV. Derra et al. (1960) find that in moderate and large defects, the murmur has a maximum lying in the 2nd-3rd intercostal space, and Downing and Goldberg (1956) found a single one of their 100 cases with a maximum at the apex, another at the level of the 3rd-4th intercostal space. Finally, 8 of Fyler et al.'s 98 patients (1958) had a maximum at the apex and 7 of these had pulmonary vascular obstruction. Particularly in Eisenmenger's complex, Kohout et al. (1955) found a typically strong harsh systolic murmur of strength 3 (of 4 possibles) in the left 3rd-4th intercostal space at the sternal border.

Selzer (1949) and P. Wood et al. (1954) found no or only slight correlation between the magnitude of the defect and the strength of the murmur, likewise none between the localization and the size of the defect or its anatomical placing. Harned et al. (1955) and Fenig et al. (1965) state that there is only a slight agreement between the strength of the murmur and the pressure gradient through the defect. The intensity of the murmur does not vary inversely with the systolic pressure in PA, as might have been expected. Hollman et al. (1963) state that in all patients except those with Roger's disease and Eisenmenger's complex, the length of the VSD murmur appears to be an excellent guide to the degree of severity of the pulmonary vascular disease. When it was pansystolic, there was rarely severe pulmonary vascular disease. In brief murmurs, there was always moderate or severe pulmonary vascular disease present.

Diastolic murmur: Two different diastolic murmurs are described, which may occur in isolated VSD. On the one hand there is a high frequency blowing decrescendo sound, most often localized to the pulmonary region, presumably a pulmonary and perhaps also an aortic failure murmur, mainly occurring in VSD patients with pulmonary hypertension, and on the other hand a mid- or proto-diastolic low-frequency rumbling murmur at the apical area (a relative or functional mitral stenosis murmur) in large left-to-right shunts and low pulmonary resistance (for literature and references see Schaefer et al. 1960, Veasy 1960, Segal and Kalman 1964).

There is no complete agreement with regard to the hemodynamic correlations to the apical diastolic murmur. Some authors find that a pronounced and prolonged diastolic apical murmur is present in large left-to-right shunts, but a short and weak murmur could occur with great pulmonary resistance (Cleland et al. 1958, Dammann et al. 1960, Derra et al. 1960).

Neill and Taussig (1959) find the apical diastolic murmur in both small and large left-to-right shunts. Fyler et al. (1958) state that the apical diastolic murmur is most often found in large left-to-right shunts without vascular pulmonary obstruction, and here this suggests a noticeable increase in heart size. Lack of diastolic apical murmur signified that there was probably a small left-to-right shunt, but said nothing about the size of heart.

With regard to the frequency of the diastolic murmurs in isolated VSD, not much is stated. P. Wood et al. (1954) found apical diastolic murmurs in 90% of the severe cases with large blood flow, 60% in the moderate cases and 10% in the slight cases. Nadas (1957) found a mid-diastolic murmur in 2/3 of his VSD patients.

Author's material

In the following, the separate anamnestic symptoms and the clinical and physical findings in the patients constituting the material will be reviewed and evaluated for their value in the diagnosis of the disease, by means of the percentage incidence with which they occur in the various degrees of severity of the disease, and by their relationship to the hemodynamic findings, namely the pressure in the RV or PA and the magnitude of the shunt through the septal defect.

Anamnestic symptoms

In what follows, anamnestic symptoms or "subjective symptoms" refer to the information about symptoms given on admission to the Queen Louise's Children's

Table. 3. Age at first cardiac symptom in relation to pressure in RV and the left-to-right shunt (expressed by decrease in oxygen saturation from RV to RA in %) in 144 children with isolated VSD, 124 of them under 2 years of age at first cardiological examination. The figures in brackets are the patients in the positions shown, in whom the disease was found by chance.

Age in months	Pressure in RV in mm Hg				Number	Oxygen deficit in RV to RA in %				total
	≤ 25	26-40	41-60	≥ 61		0-9	10-14	15-19	≥ 20	
<1	7 (2)	10 (1)	20 (2)	34 (3)		19 (3)	17 (2)	18 (2)	17 (1)	71 (8)
1	5 (3)	3 (2)	5 (3)	7		6 (1)	8 (3)	3 (2)	3 (2)	20 (8)
2-3	4 (2)	2	5 (1)	8		6	3	3 (1)	7 (2)	19 (3)
4-5	1 (1)	5 (3)	0	4 (1)		2 (2)	2 (1)	5 (2)	1	10 (5)
6-11	1 (1)	4 (2)	5 (2)	6 (1)		2 (1)	4 (2)	6 (2)	4 (1)	16 (6)
12-17	1	1 (1)	0	0		2 (1)	0	0	0	2 (1)
18-23	0	0	0	0		0	0	0	0	0
≥ 24	0	5 (3)	0	1		3 (2)	2 (1)	0	1	6 (3)
total	19 (9)	30 (12)	35 (8)	60 (5)		40 (10)	36 (9)	35 (9)	33 (6)	144 (34)
<u>total</u>										
< 6	17 (8)	20 (6)	30 (6)	53 (4)		33 (6)	30 (6)	29 (7)	28 (5)	120 (24)
< 12	18 (9)	24 (8)	35 (8)	59 (5)		35 (7)	34 (8)	35 (9)	32 (6)	136 (30)
< 24	19 (9)	25 (9)	35 (8)	59 (5)		37 (8)	34 (8)	35 (9)	32 (6)	138 (31)

Hospital (the hospitalization during which the first cardiological examination was carried out), both by the parents or other accompanying relatives, as well as by the referring doctor or possibly other hospitals.

Age at first cardiac symptom

Table 3 shows the age at which the first cardiac symptom was observed (in relation to the hemodynamic conditions at the first cardiological examination). The table shows that of the 144 patients constituting the material, 138 had had their first cardiac symptom noticed before the age of 2 years, and in 120 of the 144 the first cardiac symptom has been noticed before the age of 6 months. As the table shows, it does not appear as if those patients who might be expected to have their symptoms early (patients with high pressure in the RV or PA, and patients with a large left-to-right shunt) have actually had their symptoms earlier than patients with the milder hemodynamic changes.

Reasons for referral

The question as to the reason for referral on admission to hospital is also of interest. While murmurs heard at birth or on the occasion of the first prophylactic examinations, just as signs of heart disease noticed in connection with other diseases, need not necessarily have been associated with such a poor condition in the patient as to lead to an early admission, nevertheless symptoms such as, in particular, failure to thrive and dyspnoea, have led to admission at a quite early stage.

Comparing the reasons for referral with the hemodynamic conditions (at the first cardiological examination), it is particularly circumstances such as treatment for pulmonary infections (with as a result the discovery of the heart disease), failure to thrive and dyspnoea, which appears to be correlated to the hemodynamically most severe cases, this being the case in particular for the correlation of the symptoms with the magnitude of the pressure in the right half of the heart. One point should be noted: the 4 patients who had the smallest left-to-right shunt, and in whom the main reason for referral was cyanosis (cases nos. 479, 686, 721 and 815) had a systolic pressure in the RV or PA of 54, 21, 39 and 24 mm Hg, respectively, so that the cyanosis, at any rate in the case of three of them, cannot have been caused by a high pulmonary vascular resistance + high pressure in the RV or PA, and in consequence by a right-to-left shunt.

Review of the separate anamnestic symptoms and the clinical and physical findings

A detailed review will now be given of the separate anamnestic symptoms, and in particular the clinical and physical findings.

Subjective and anamnestic symptoms

Failure to thrive (i. e. hindered or possibly interrupted increase in length and weight) is one of the most common complaints among the subjective symptoms which are encountered in the disease picture of isolated VSD in its more severe forms. Failure to thrive - possibly together with other symptoms - is often the reason for the medical examination and a subsequent admission to hospital.

"Tachypnoea at rest" and "tachypnoea on effort" (i. e. nursing, washing, feeding and crying) need no special comments.

"Cyanosis at rest" and "cyanosis on effort" most often cover peripheral and central cyanosis, which could not be distinguished anamnesticly.

The concept "reduced endurance in feeding" in this material covers patients who in particular have difficulty in ingesting a normal volume of food per meal, or where feeding has to be interrupted several, perhaps many times during each meal.

"Recurrent lung infections" speak for themselves, but it should be mentioned that it is not only a question of a particular patient being specially susceptible to respiratory tract infections, but also having difficulty in getting rid of pneumonia, bronchitis or the like when once acquired, and that these infections in the lungs often replace each other, so that the patient has more or less pronounced lung symptoms almost permanently.

"Other symptoms" were found in 4 patients, comprising: pronounced palpitation in one (no. 826), precordial pain in one (no. 554), pronounced pallor in one (no. 5) and rapid heart action in one (no. 387).

"Disease discovered by accident" = no anamnestic symptoms.

Clinical and physical findings

Apart from length or height and weight reports, the clinical and physical findings discussed below originate from the first cardiological examination which was made in all cases by the permanent cardiological consultant of the hospital (Ib Boesen, M.D.). This should give the greatest possible chance of obtaining

a uniform objective evaluation of the patients. Only in rare cases have the symptoms which the permanent hospital staff of doctors observed on admission been included in order to supplement the evaluation by the specialist, e.g. in those cases where after admission, but before the examination by the specialist, the patient has been digitalized, being in such a poor condition that it was considered dangerous to wait until the specialist's examination had taken place. In such cases, appropriate attention has been paid to the evaluation of the untreated patient by the first doctors making an examination.

"Tachypnoea at rest" and "tachypnoea on exertion" have not been graduated any further than this. Especially in the severe cases of the disease, there has often been complicating pneumonia or bronchitis, which has affected the rate of respiration, so that it was not considered possible on the basis of the clinical and physical evaluation to make any further grading of the tachypnoea.

"Cyanosis at rest" and "cyanosis on exertion" have likewise not been graded any further, for the same reasons. Furthermore, actual exercise tests were not possible on account of the age of the patients.

"Failure to thrive" is defined in this study as a state in which the patient's weight is reduced to or below a value which is 10% below the weight for age.

"Poor growth" is a term which is used to indicate that the length or height for weight of the patient is equal to or less than a value which is 10% below the calculated length or height for weight. (The term has been found necessary, since as will appear later, height is influenced by the disease to a lesser degree than weight).

The norms used for weight and length or height for the age group 0-1 year are those of Ryssing (1959), which take into account the birth weight of the infant and the sex. For ages from 1 year upwards, the figures given by O. Andersen (1961) have been used (which only deviate to a slight degree from the values given by Sundal in *Nordisk Lærebog i Pædiatri* (1967) and in Nelson's *Textbook of Pediatrics* (1959)). In addition, those values have been employed which have been used as normal values in the daily work at the Queen Louise's Children's Hospital.

In the graphical presentation of the relationship between length or height, and age, the diagrams prepared by Karlberg et al. (1959) have been used, showing the mean value for boys and girls, and $\pm$ twice the standard deviation, covering a total of 95% of the normal range. In the graphical presentation of the weight of the infant in relation to the normal weight, 2 concepts for normal values have been employed: the weight for age, i.e. the weight corresponding to the chronological age of the infant, and the weight for height, i.e. the weight calculated according to the actual length or height of the infant. In both cases, the weight norms indicated above have been used as normal values, but in the

graphical presentation, preference has been given to a coordinate system with normal value as a 0-line parallel to the abscissa (age being marked off along the abscissa) and with the percentage deviation from normal marked off on the ordinate, precisely because of the dependence of the weight on the weight at birth. Karlberg et al. (1959) give no normal curves for weight according to age. The diagrams in Nelson's Textbook of Pediatrics (1959) have been constructed for both boys and girls; however, if one had constructed diagrams for boys and girls on the basis of the tables given in this book, no allowance would have been made for the influence of birth weight on the weight during the first years of life, which is the age period of special interest in the present study. The position is the same in the case of Nordisk Lærebog i Pædiatri (1967).

Thus, in the case of each infant, the weight for age difference and the weight for length difference have been calculated as differences from the normal weight for age and weight for length, and these differences have then been expressed as a percentage of the normal weight for age and weight for length. These percentage deviations have been used in the graphic representation as expressing the retardation of growth (if such is present). An arbitrary limit has been put at -10% for weight for age and weight for length, and, as mentioned, a weight for age $\bar{x}$ -10% of the normal has been designated as "failure to thrive", while a weight for length $\bar{x}$ -10% of normal has been designated as "failure to grow", since failure to thrive and failure to grow do not occur with equal frequency. The limit of -10% used was presumably chosen too small in the original planning of the investigation; if the weight values in Nelson's Textbook of Pediatrics (1959) are used, and the 10th percentile values are calculated as percentage of the mean values for different ages, then the lower limit - calculated for both sexes together - should have been about -12.5%, if it should have corresponded to the lower limit for 80% of the normal values. The percentage deviation of a definite proportion of the normal values from the mean value is maintained almost constant up to a point between the age of $4\frac{1}{2}$ and 5 years, after which the lower limit for this same proportion of the normal values slowly, and to an increasing degree, bends away from the mean value, so that instead of a lower limit of -10% for the age of 0-5 years, there is a lower limit of -14% of the mean value at the age of 13 years. This state of affairs is indicated in the growth figures, and in the question of + or - growth retardation in the age groups over the age of 5 years, which is of special interest for the analysis of the follow-up results.

Other circumstances will be mentioned which affect the ability to thrive and deviations from this (in both length and height as well as weight). In addition to their heart disease, a number of the patients in the material have also other di-

Table 4. The incidence of the subjective and anamnestic symptoms at the first cardiological examination, in 144 children with VSD, in relation to the pressure in the right side of the heart.

Symptom	Total in all	≤ 25 mm		26-40 mm		41-60 mm		≥ 61 mm	
		< 2 years		< 2 years		< 2 years		< 2 years	
		total	< 2 years	total	< 2 years	total	< 2 years	total	< 2 years
Failure to thrive	88	19	15	30	20	35	34	60	55
Tachypnoea at rest	41	7	6	13	10	19	19	49	47
Tachypnoea on effort	79	1	1	3	3	15	15	22	21
Cyanosis at rest	5	4	3	13	9	22	22	40	38
Cyanosis on effort	45	1	1	0	0	1	1	3	2
Reduced endurance	14	3	3	3	2	14	14	25	23
Recurrent pulmonary infections	38	2	0	5	3	2	2	5	3
Other symptoms	4	1	1	6	5	11	11	20	20
Disease found by chance	34	1	0	1	1	1	1	1	1
		9	7	12	6	8	7	5	4

Table 5. The incidence of the subjective and anamnestic symptoms at the first cardiological examination, in 144 children with VSD, in relation to the magnitude of the left-to-right shunt (expressed by decrease in oxygen saturation from RV to RA in %).

Symptom	Total in all	0-9%		10-14%		15-19%		≥ 20%	
		< 2 years		< 2 years		< 2 years		< 2 years	
		total		total		total		total	
Failure to thrive	88	40	31	36	20	23	22	33	21
Tachypnoea at rest	41	8	8	8	8	10	10	15	14
Tachypnoea on effort	79	20	18	16	14	22	20	21	20
Cyanosis on effort	5	1	1	0	0	2	2	2	1
Reduced endurance	45	8	8	10	8	14	14	13	12
Recurrent pulmonary infections	14	5	2	3	1	1	1	5	4
Other symptoms	38	7	6	8	8	12	12	11	11
Disease found by chance	4	1	0	1	1	0	0	2	2
Disease found by chance	34	10	5	9	6	9	7	6	6

seases, and in those cases where the accompanying diseases may have contributed to a possible failure to thrive, this has been indicated in the graphic illustrations. Furthermore, it was not considered possible to use the norms employed for length and weight in the case of 4 Greenlanders in the material, so that in the graphic representation these have also been marked in the same way as the infants with accompanying diseases which are of significance for the ability to thrive. Finally, for use later on in the study, the diagrams show whether the patients were or were not operated on for the heart disease following the first cardiological examination.

"Voussure" and "thrill" are only stated as being present or not, without any further grading of degree of severity.

"Murmur" (systolic and possibly diastolic) has been graded in the following terms: "weak" (= strength 1-2 of a total of 6 grades of strength), "moderately strong" (= strength 3), "moderately strong - strong" (= strength 4), "strong" (= strength 5) and "very strong" (= strength 6). The verbal designations of strength have been used in this study, because these were used in the descriptions during the investigations of the first few years, but according to discussions with the cardiological specialist, they correspond to the numerical designations of strength which have been used in recent years.

"Rales on pulmonary stethoscopy (p. st)" has only been indicated as present or not, but not graded.

"Liver $\bar{>}$ 1 $\frac{1}{2}$ finger-widths under the costal margin" has been set as the limit for what may be regarded as a definitely enlarged liver.

"Edema" is included in the tables for the sake of completeness, even though the first cardiological examinations showed no edema in the patients of the material.

In what follows, an evaluation will be made of the incidence of the anamnestic symptoms and the clinical and physical findings in the present material, and the relationship between the incidence of their occurrence and the degree of severity of the disease.

The incidence of the separate anamnestic symptoms at the first cardiological examination is shown in table 4, correlated with the pressure in the RV or PA, and in table 5 correlated with the magnitude of the left-to-right shunt. The tables show that the 5 most important anamnestic symptoms by incidence are "failure to thrive", "tachypnoea on effort", "cyanosis on effort", "tachypnoea at rest", and "recurrent pulmonary infections". It is seen that when these symptoms are correlated with the pressure in the RV or PA and with the size of the shunt, there is a clear relationship between the incidence of the symptoms and the magnitude of the pressure in RV or PA, but this is the case only to a slight degree in correlation with shunt size.

Another question examined is whether the presence of more of the frequently occurring anamnestic symptoms suggests the disease to be more severe, judged on the basis of the pressure in the right half of the heart and the magnitude of the shunt through the ventricular septal defect. Table 6 shows that the greater the number of anamnestic symptoms found in a patient, the more pronounced are the hemodynamic changes. This holds both for the correlation of the incidence of symptoms with magnitude of pressure in RV or PA as well as with shunt size, but the correlation seems more pronounced in the case of the pressure value. Roughly speaking, the position is that in patients with a systolic pressure in the RV or PA ≥ 41 mm Hg, or a shunt size which when expressed by oxygen saturation deficit RV to RA in per cent is $\geq 15\%$, 3 out of the 5 symptoms mentioned are found in more than half of the patients.

The incidence of the separate clinical and physical findings at first cardiological examination is shown in table 7, correlated with the magnitude of the pressure in the RV or PA, and in table 8 correlated with the magnitude of the shunt through the septal defect. These tables show that the most commonly occurring clinical or physical finding is "systolic murmur" (present in all the patients of the material with exception of 3). Thereafter, "failure to thrive", "tachypnoea on effort", "tachypnoea at rest", "hepatomegaly" and "voussure" are among the most common findings showing an increasing incidence with increasing pressure in RV or PA, while the increase in incidence with increasing size of shunt is much less pronounced.

Also in the case of the clinical and physical findings, the question has been examined whether the presence of more of these frequently occurring findings suggests more severe disease than if a smaller number of these findings are present in the patient. This problem is elucidated in table 9. It appears from this table (just as it appeared from the corresponding table no. 6 for the anamnestic symptoms), that the greater the number of frequently occurring clinical and physical findings in the patient, the more serious is the case when evaluated on the basis of the hemodynamic conditions. This is true both when the findings are related to the size of shunt and to the size of the pressure in RV or PA, but is most pronounced in the latter case. It should be added that presence of a systolic murmur has not been included in table 9, as it has been found in all patients at first cardiological examination (with the exception of 3). The table shows that in patients with a pressure in the right half of the heart ≥ 61 mm Hg, 4 out of the 5 symptoms tabulated are found in almost 3/4 of the patients, and with a shunt size $\geq 15\%$, 4 out of the 5 symptoms tabulated are found in more than half of the patients.

Table 6. Number of patients under 2 years of age with isolated VSD, who had 2, 3, 4 or 5 of the most important subjective and anamnestic symptoms (i. e. symptoms which showed the most pronounced increase in incidence with increase in size of left-to-right shunt and increase in magnitude of pressure in RV), at the first cardiological examination.

Symptoms	Total	Size of left-to-right shunt (oxygen deficit from RV to RA in %)			
		0-9%	10-14%	15-19%	≥ 20%
Failure to thrive	80	18	17	22	23
Tachypnoea at rest	55	9	11	17	18
Tachypnoea on effort	21	2	3	9	7
Cyanosis on effort	7	1	1	2	3
Recurrent pulmonary infections					
Of total of patients	124	31	30	32	31

Symptoms	Total	Magnitude of pressure in RV in mm Hg			
		0-25	26-40	41-60	≥ 61
Failure to thrive	80	3	10	23	44
Tachypnoea at rest	55	1	4	18	32
Tachypnoea on effort	21	0	1	6	14
Cyanosis on effort	7	0	0	3	4
Recurrent pulmonary infections					
Of total of patients	124	15	20	34	55

Table 8. Incidence of the clinical and physical findings at first cardiological examination, in 144 children with VSD, in relation to the magnitude of the left-to-right shunt (expressed as oxygen deficit from RV to RA in %).

[illegible]

Table 9. Number of patients under 2 years of age with isolated VSD who had 2, 3, 4 or 5 of the most important clinical and physical findings (i. e. symptoms showing the greatest increase with increase in size of left-to-right shunt or magnitude of pressure in the RV), at first cardiological examination.

Symptoms	Total	Size of left-to-right shunt (oxygen deficit from RV to RA in %)			
		0-9%	10-14%	15-19%	≥ 20%
Tachypnoea at rest	92	14	23	29	26
Tachypnoea on effort	79	10	20	26	23
Failure to thrive	58	8	14	20	16
Voussure	22	3	2	9	8
Liver $\geq 1\frac{1}{2}$ finger-widths under costal margin					
Of total of patients	124	31	30	32	31

Symptoms	Total	Magnitude of pressure in RV in mm Hg			
		0-25	26-40	41-60	≥ 61
Failure to thrive	92	3	9	29	51
Tachypnoea on effort	79	3	4	26	46
Failure to thrive	58	1	3	15	39
Voussure	22	0	2	2	18
Liver $\geq 1\frac{1}{2}$ finger-widths under costal margin					
Of total of patients	124	15	20	34	55

Failure to thrive

If the anamnestic reports of failure to thrive are correlated with the hemodynamic studies made later, then, as mentioned, failure to thrive is found with increasing frequency with increasing pressure in RV or PA, whereas correlation with the various shunt sizes is not striking (tables 4 and 5).

Considered as a clinical or physical finding, it has been possible to group failure to thrive into disturbances in weight and disturbances in length or height, and again in the case of weight, into weight for age and weight for height. Diagrams have been drawn for the actual weight for age and weight for length at first cardiological examination for all patients, both in relation to magnitude of pressure in the right half of the heart (figures 1 and 2), and in relation to magnitude of the shunt through the septal defect (figures 3 and 4). The dependence of weight for age on pressure in RV or PA, and to a lesser degree the dependence of weight for height (figures 1 and 2), is pronounced; the greater the pressure in the right half of the heart, the greater the retardation in weight. The dependence of weight for age and likewise weight for height on the various magnitudes of shunt through the septal defect (figures 3 and 4) shows no definite tendency. It may be assumed that a small pulmonary vascular resistance, in the case of pressure equalization between RV and LV, will be reflected in a large left-to-right shunt, and conversely. In figure 5, therefore, in the case of weight for age, where the weight deficit is most pronounced when considered in relation to the pressure in RV or PA, the 55 patients under the age of 2 years with such a high pressure in RV or PA ($\bar{S}$ 61 mm Hg) that a pressure equalization may be considered to exist between the two ventricles, have been grouped into different shunt-size groups, to examine whether a large pulmonary resistance (corresponding to small left-to-right shunt) might be accompanied by a greater inhibition in weight, than a small pulmonary resistance. Such a difference, however, could not be demonstrated at the first cardiological examination, although reference should be made to the results of the follow-up examination (figure 14, page 117). The number of diagrams has been restricted in the case of recordings of length or height. The influence of the various shunt sizes on length or height, evaluated from a comparison between weight for age and weight for length, appears to depend very slightly indeed on size of shunt, compared to the dependence on pressure in the right half of the heart. Length or height value in relation to normal length or height in the various patients in the material has therefore only been recorded in relation to the different pressure values in the right half of the heart, (figures 6, 7 and 8). The inhibition in length at various pressure values is not striking; it is only more or less pronounced in the case of girls with presumed pressure equalization between RV and LV (figure 8).

In the present material, the conditions with regard to the ability to thrive correspond well to those demonstrated by most authors (for literature and references see Ash 1964, Maranhao 1965). On the other hand, as mentioned, it has not been possible to demonstrate that retardation in growth at the first cardiological examination was more pronounced in the case of high pulmonary resistance than in the case of low pulmonary resistance, as found by Fyler et al. (1958), Blount and Woodwark (1960), Hilger and Schaede (1960) and Veasy (1960). (See, however, the follow-up examination, page 117, figure 14). The explanation put forward by Howitt and Wade (1962) and Walker et al. (1965), that retardation in growth should be due to the low systemic flow, does not agree with the findings by the above authors that the greatest retardation in growth takes place at the highest pulmonary resistance. If the 55 infants under the age of 2 years in the material with presumed pressure equalization between RV and LV, are examined for the significance of recurrent respiratory tract infections for retardation of growth increase, it appears that 20 have anamnestic data on recurrent respiratory tract infections, and these had a weight which was on the average 22.2% under normal (or if 4 of the patients are omitted who had other accompanying diseases of significance for the ability to thrive, 19.8% under normal), while the 35 for whom there was no information on recurrent infections of the respiratory tract, had a weight which on the average was 26.2% below normal (or if 7 of the patients are omitted who had other accompanying diseases of significance for the ability to thrive, 26.6% below normal). This material thus provides no support for the theory put forward by F. H. Adams et al. (1954) that retardation of growth can be avoided in patients with congenital heart disease with a left-to-right shunt, if they are kept free from recurrent respiratory tract infections.

Tachypnoea at rest and on effort

Tachypnoea at rest and on effort, both as an anamnestic symptom and as a clinical finding, have been noticed frequently in the material in the present study, and the incidence appears to increase with increasing pressure in the RV or PA, whereas no definite correlation is found between the incidence of the symptom tachypnoea at rest and on effort, and the magnitude of the left-to-right shunt. This is in agreement with what most authors report (Heath and Whitaker 1956, Hubbard et al. 1957, Neill and Taussig 1959, Schaede et al. 1960, Ritter et al. 1965), and does not support the view of Derra et al. (1960), that the most important cause of tachypnoea is the large left-to-right shunt. As mentioned by Merrild (1962), Lind has suggested that the tachypnoea is due

Fig. 1. Weight at first cardiological examination, as percentage deviation from weight-for-age, for different pressures in the RV, in 144 children with VSD, 124 of them under 2 years of age at first examination.

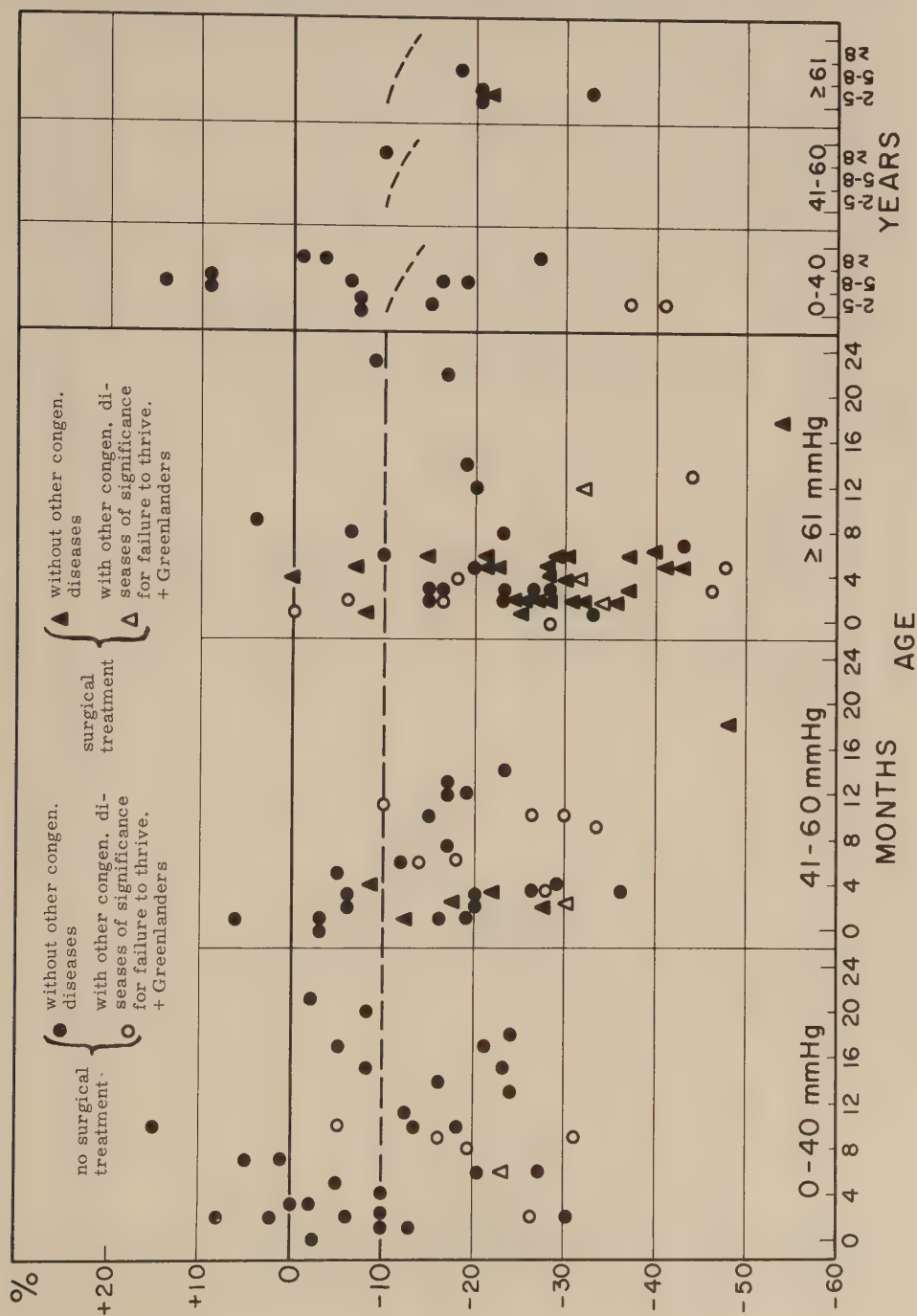


Fig. 2. Weight at first cardiological examination, as percentage deviation from weight-for-height, for different pressures in the RV, in 144 children with VSD, 124 of them under 2 years of age at first examination.

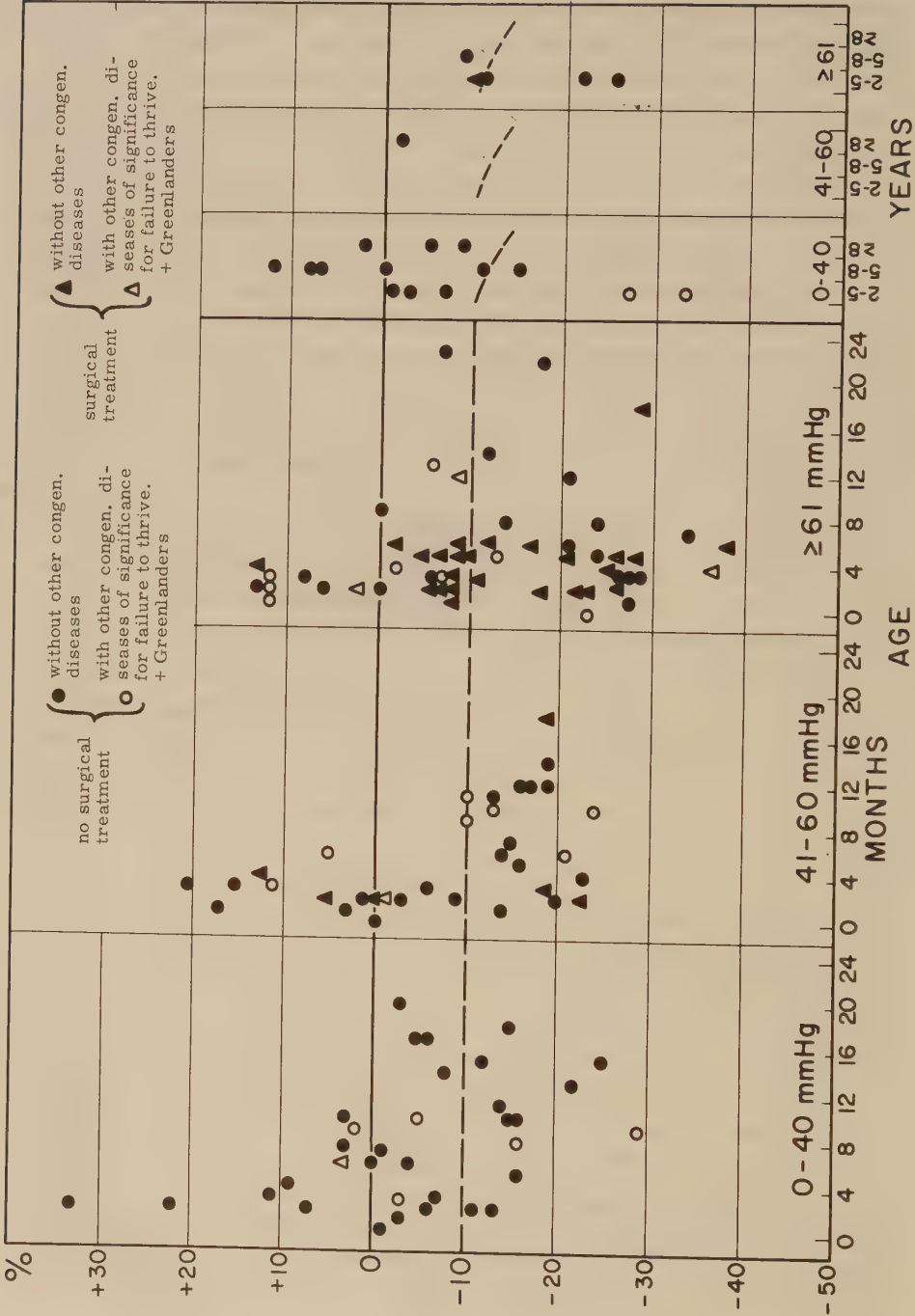


Fig. 3. Weight at first cardiological examination, as percentage deviation from weight-for-age, for different sizes of shunt (decrease in oxygen saturation from RV to RA in %), in 144 children with VSD, 124 of them under 2 years of age at first examination.

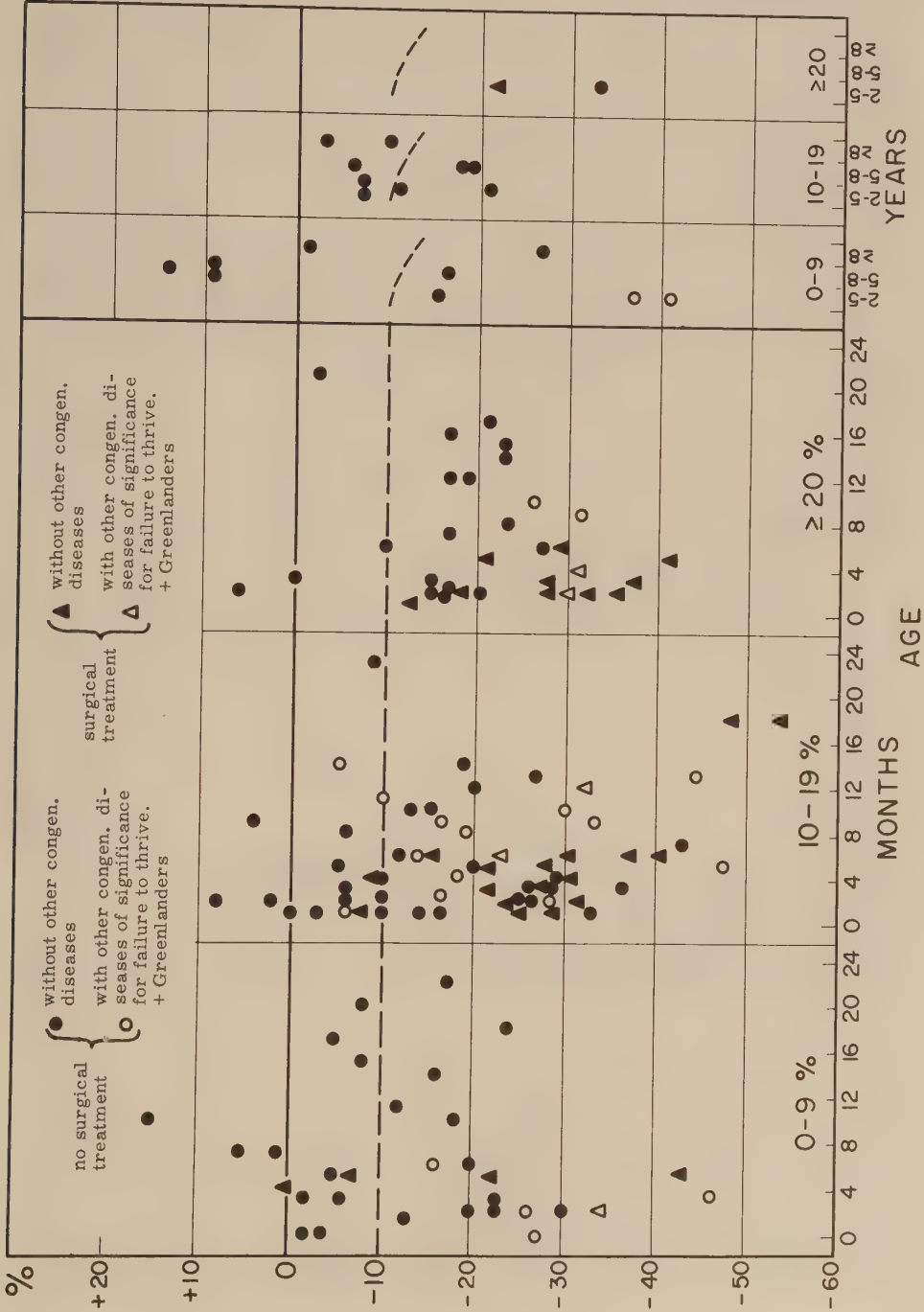


Fig. 4. Weight at first cardiological examination, as percentage deviation from weight-for-height, for different sizes of shunt (decrease in oxygen saturation from RV to RA in %), in 144 children with VSD, 124 of them under 2 years of age at first examination.

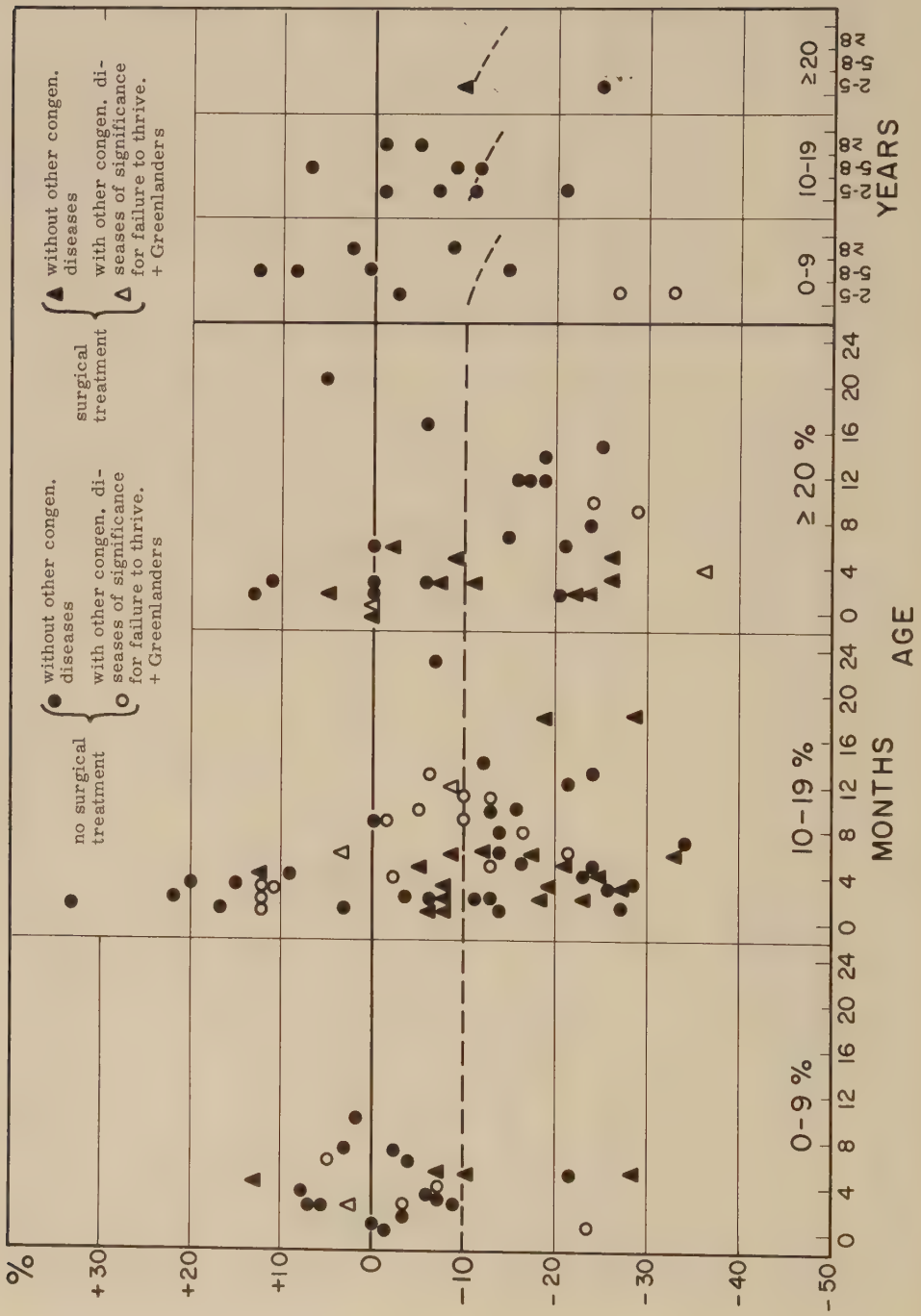


Fig. 5. Weight at first cardiological examination, as percentage deviation from weight-for-age, in 55 children under 2 years of age with isolated VSD and a pressure in the RV ≥ 61 mm Hg, grouped according to different sizes of shunt (1/different values of pulmonary vascular resistance). The sizes of the shunts in the 3 groups are expressed by the decrease in oxygen saturation from RV to RA in %, 0-9%, 10-19% and $\geq 20\%$ respectively.

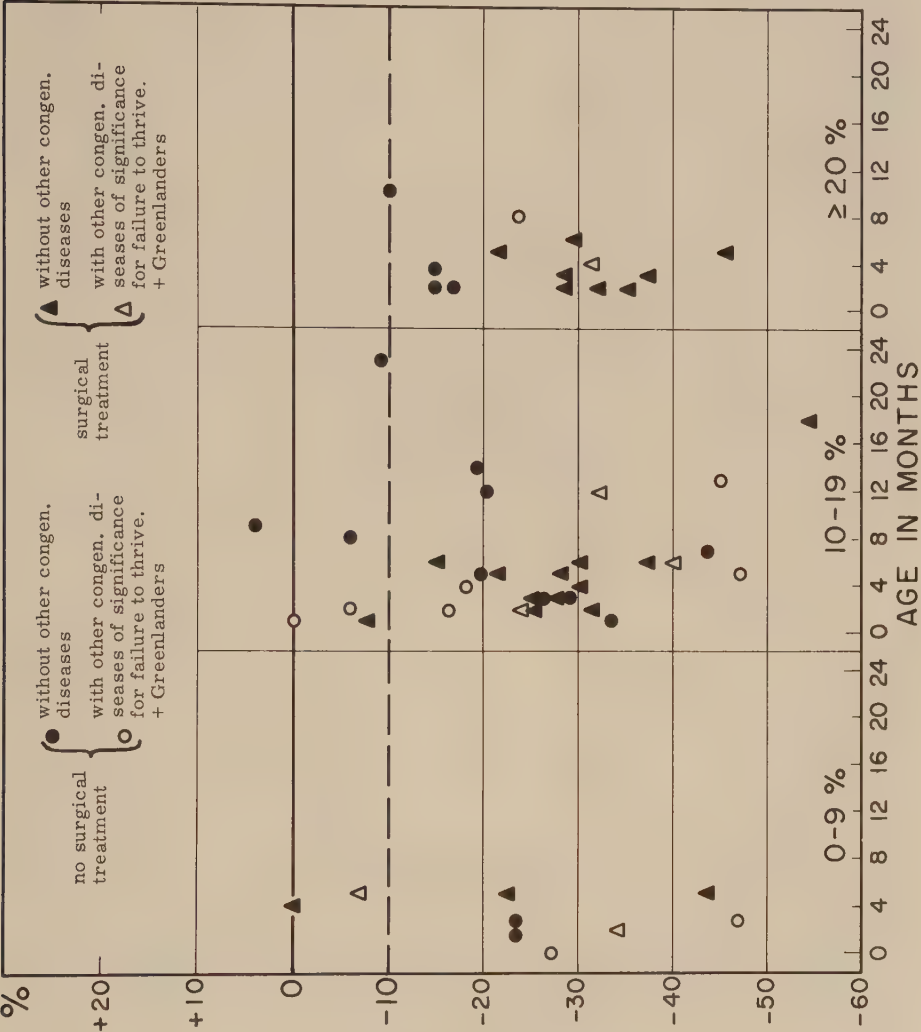


Fig. 6. Relationship between height and age, compared to normal subjects, in 36 girls (27 under 2 years of age) and 13 boys (8 under 2 years of age) at first cardiological examination, all patients with a pressure in the RV ≥ 40 mm Hg.

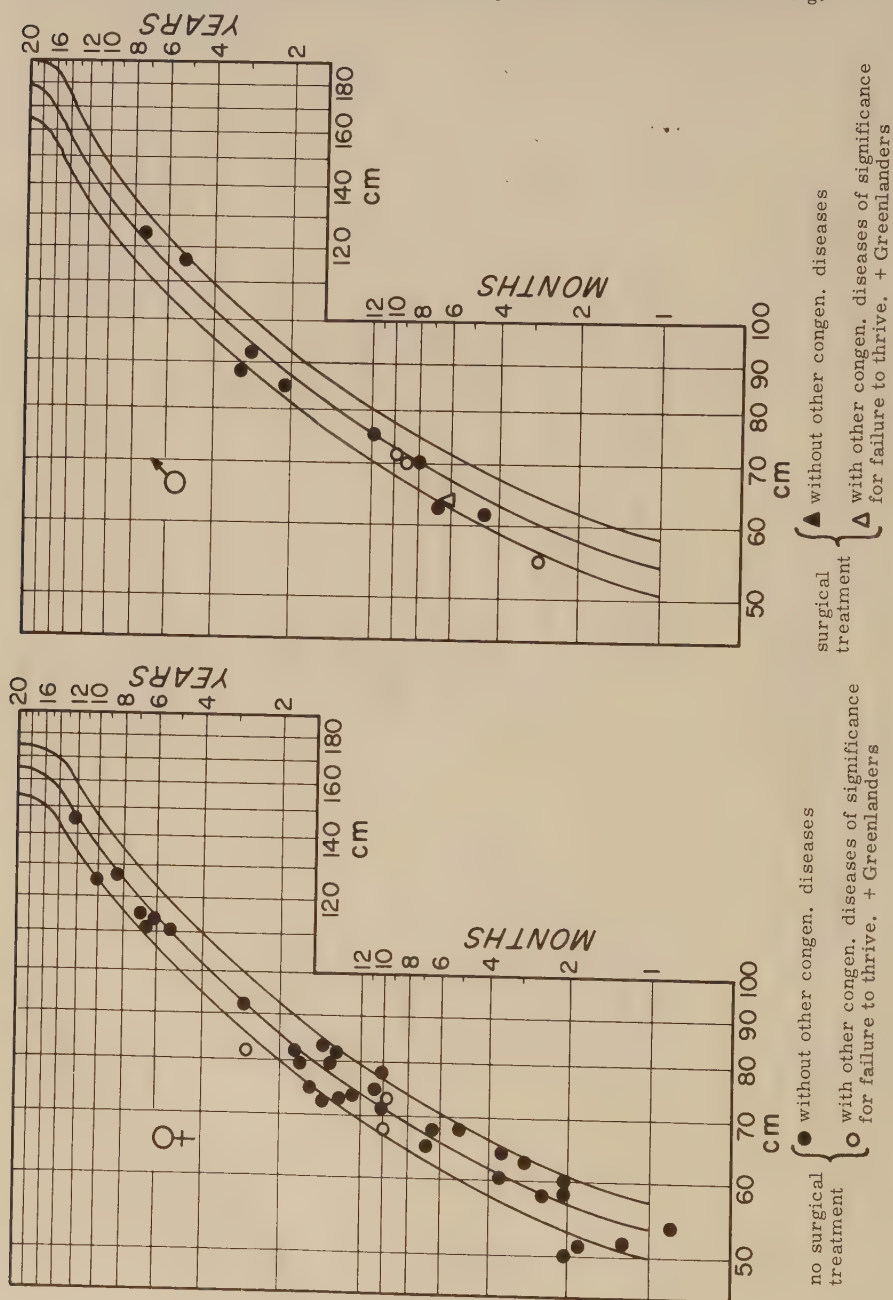


Fig. 7. Relationship between height and age, compared to normal subjects, in 17 girls (16 under 2 years of age) and 18 boys (all under 2 years of age) at first cardiological examination, all patients with a pressure in the RV of 41-60 mm Hg.

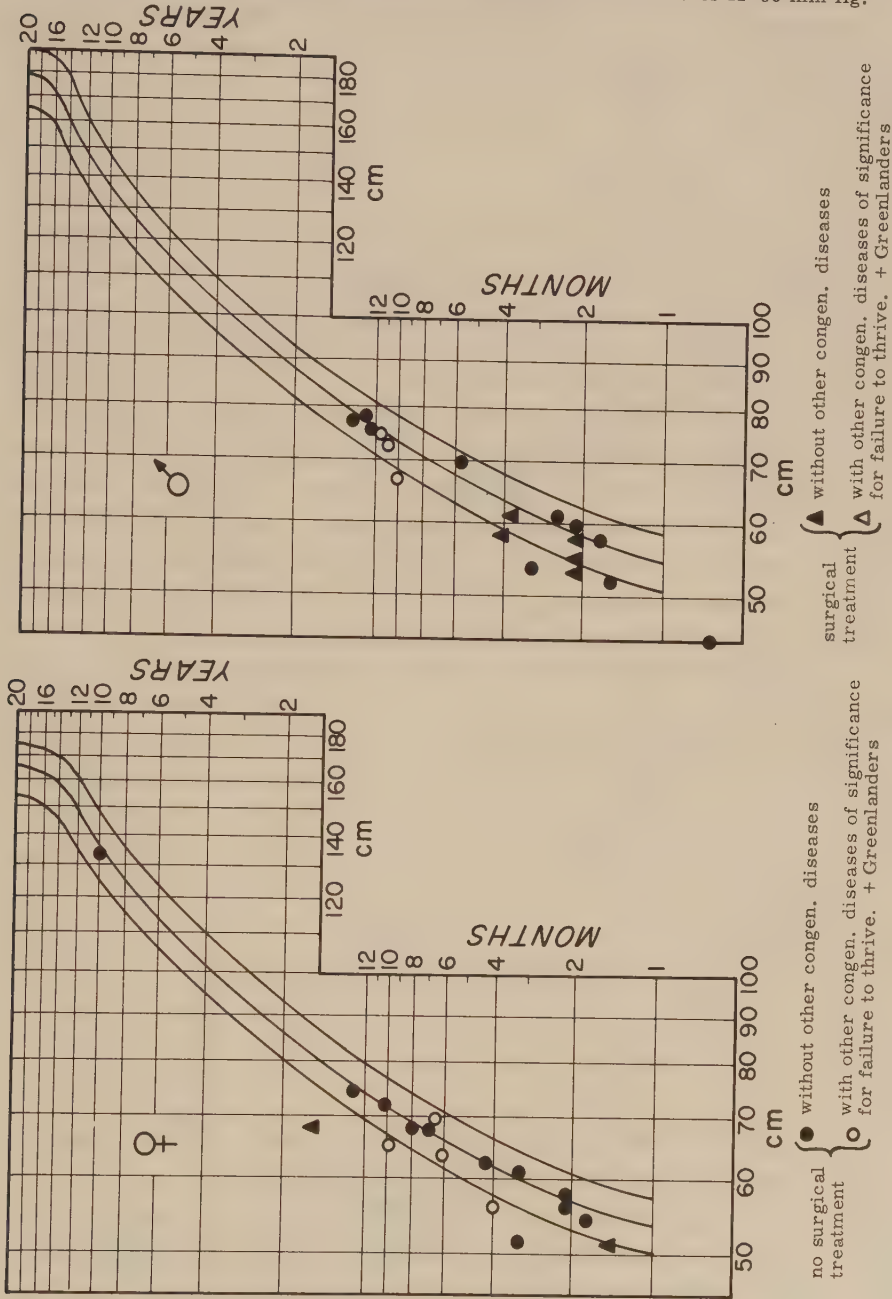
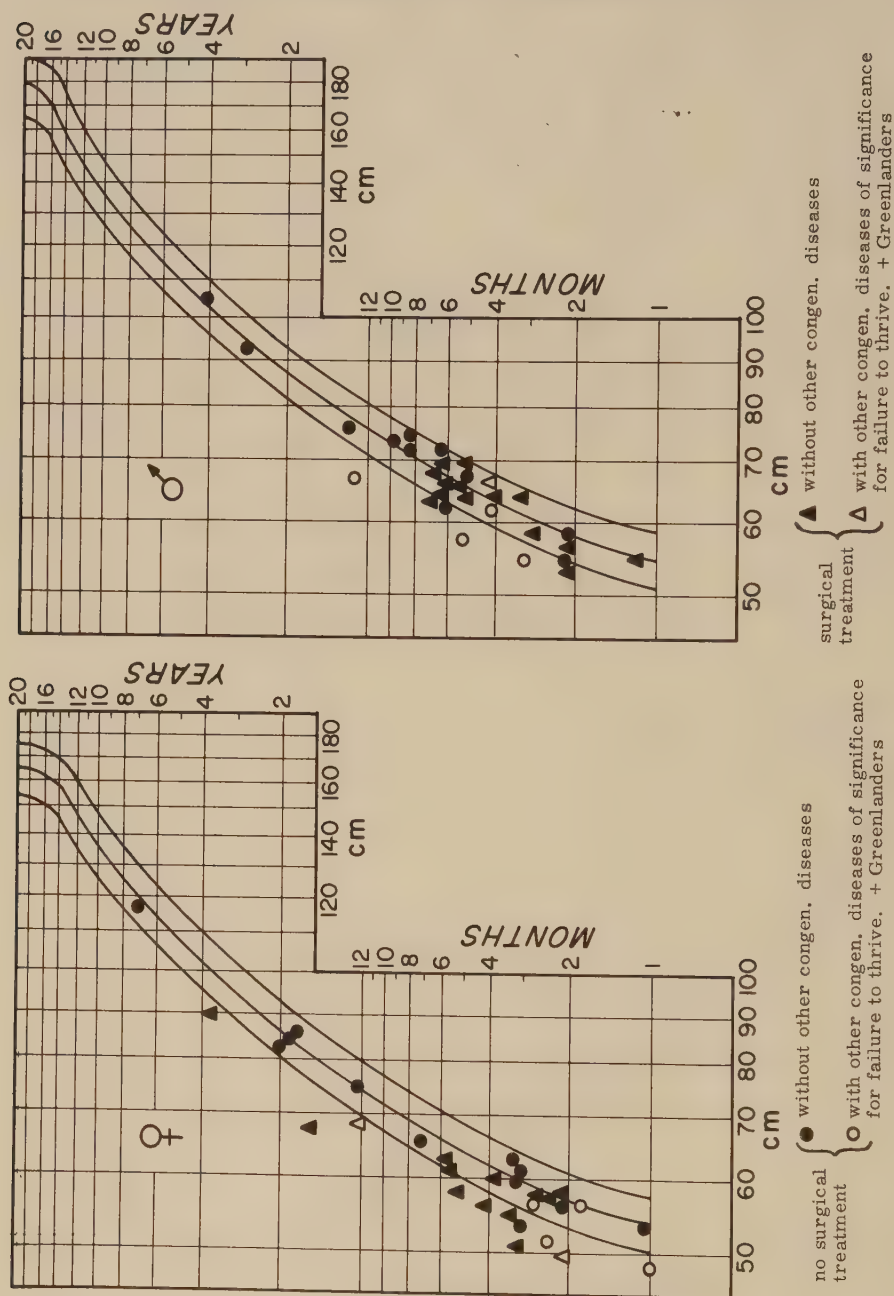


Fig. 8. Relationship between height and age, compared to normal subjects, in 30 girls (27 under 2 years of age) and 30 boys (28 under 2 years of age) at first cardiological examination, all patients with a pressure in the RV ≥ 61 mm Hg.



to the large heart, which occupies so much space that it reduces the lung capacity. Support for this has been found in Merrild's material and also in the present material, see table 10, where there is a clear rise in resting tachypnoea and tachypnoea on effort, with rising relative heart volume.

Cyanosis at rest and on effort

Cyanosis as an "anamnestic" symptom occurs most frequently in the form of effort cyanosis (table 4, page 37). It has not been possible to distinguish central from peripheral cyanosis, but if it has been a question mainly of central cyanosis, then from the hemodynamic studies there is nothing to contradict the possibility that many of these patients may have had such a high pressure in the right half of the heart, that there may have been reversal of the left-to-right shunt to a right-to-left shunt, at any rate intermittently. In the case of cyanosis as a clinical finding (table 7, page 38), the same may be the case; there were 16 patients under the age of 2 years who had cyanosis on effort, 15 of them with a pressure in the RV or PA $\geq$ 41 mm Hg; in other words, as pointed out by Walker et al. (1965), with a possibility of pressure equalization between the two ventricles (the lowest pressure was 48 mm Hg), especially in the case of cyanosis on effort, where it is most pronounced (Veasy 1960). The right-to-left shunt through the septal defect may thus be regarded as a sequel to a delayed regression of the fetal high pulmonary vascular resistance, possibly continuing in the direction of increasing cardiac failure, or towards the development of a severe pulmonary hypertension, as suggested by Nadas (1957), Fyler et al. (1958), Keith et al. (1958), Dammann et al. (1960) and Walker et al. (1965). Of the 13 infants under the age of 2 years with cyanosis on effort, in whom information was missing with regard to the degree of oxygen saturation in the LA, 7 had signs of cardiac failure in the form of hepatomegaly.

Cardiac failure

Cardiac failure as a clinical and physical finding has presented almost exclusively in the form of hepatomegaly (liver $\geq$ 1 $\frac{1}{2}$ finger widths below the costal margin). In patients examined before the age of 2 years, hepatomegaly was found in 41.9%, in other words very frequently, as has been suggested by several authors (for literature and references see Ash 1964, Hoffman and Rudolph 1965 and Ritter et al. 1965). With regard to the time of onset of the first sign of the congenital heart disease, it may be stated that of the 7 premature infants with signs of

cardiac failure on admission, 6 had already developed their first sign of heart disease before the age of 1 month and the last at the age of 3 months, while in the case of the 45 full-term infants with signs of heart failure on admission, 26 (not quite 58%) had developed their first cardiac symptom before the age of 1 month, 4 at the age of 1 month, 5 at the age of 2-3 months, 6 at the age of 4-5 months and 4 after the age of 6 months. This appears to confirm the report by Hoffman and Rudolph (1965) that cardiac failure appears more early in premature infants than in full-term infants. In the present study, the number of cases with cardiac failure increases with the pressure in the RV or PA (table 7, page 38) (corresponding to the findings by Kaplan et al. 1963), while the dependence of cardiac failure on shunt size is very uncertain (table 8, page 38). Finally, it should be added that no edema was found in any of the cases at the first cardiological examination.

Reduced endurance in feeding

Reduced endurance in feeding does not occur particularly frequently in the present study, possibly because a large proportion of the patients in the material have been so small that the reduced endurance could only be demonstrated by their taking longer time to drink and having to have longer pauses during meals, each of which can be found associated with other states than cardiac. This symptom appears to occur to a higher degree with large left-to-right shunts (table 5, page 37) than with high pressure in the right half of the heart, but the absolute figures are too small to be considered decisive.

Recurrent lung infections

Recurrent lung infections as a clinical finding occur rather frequently in the material (in not quite 30% of the infants examined for the first time before the age of 2 years).

Deformation of the thorax

Deformation of the thorax (apart from voussure) has not been noted in the patients in this material.

Table 10. Relationship at first cardiological examination between relative heart volume (vol. /m²) and the presence of tachypnoea at rest and on effort, in 105 out of 124 children with isolated VSD who were under the age of 2 years at first examination (the heart volume could not be calculated in 19 children).

Heart vol. /m ² in ml	total	tachypnoea at rest	tachypnoea on effort
≤ 299	16	5	6
300-399	27	14	14
400-499	31	25	25
500-599	22	20	20
≥ 600	9	8	9
Total	105	72	74

Table 11. Occurrence of voussure and thrill in 124 children with isolated VSD, under the age of 2 years at first cardiological examination.

Age in months at first examination	total	voussure	thrill
< 1	3	0	0
1	9	2	0
2-3	41	15	6
4-5	18	9	1
6-11	32	8	11
12-17	14	5	12
18-23	7	4	2
Total	124	43	32

Table 12. Relationship between incidence of voussure and heart size per m² body surface in 102 children with isolated VSD, examined for the first time aged 1 to 23 months. (Of the total under 2 years of age at first examination, 19 patients were excluded as their heart volume could not be calculated, no lateral exposures of the heart having been taken, and 3 patients were excluded who were examined for the first time aged less than 1 month, as table 11 indicates that voussure can hardly have had time to develop within the first 3-4 weeks.)

		Volume of heart per m ² body surface, in ml.			
		≤ 399	400-499	500-599	≥ 600
+ voussure	33	4	10	10	9
- voussure	69	36	21	12	0
Total	102	40	31	22	9

Table 13. Relationship between maximum strength of the VSD murmur and the presence of thrill, in 121 of the 124 children with isolated VSD in the material, who were under 2 years of age at first examination. Three children without murmur are excluded.

	Strength of murmur					total
	weak	moderate	moderate to strong	strong	very strong	
+ thrill	0	2	0	25	5	32
- thrill	4	23	13	48	1	89
total	4	25	13	73	6	121

Table 14. The relationship between the strength of the systolic murmur and the localization of its maximum, in 121 children under 2 years of age at first cardiological examination. Three of 124 children had no murmur. The figures marked x show the number of those in whom a diastolic murmur was also heard.

Localization of the murmur (maximum)	Strength of murmur					total
	weak	moderate	moderate to strong	strong	very strong	
lower left sternal border	2	9	7	58 ^{5x}	6 ^{1x}	82 ^{6x}
upper left sternal border	0	0	1	1	0	2
diffusely along left sternal border	1	10 ^{2x}	3	5 ^{1x}	0	19 ^{3x}
diffusely over entire precordium	0	5 ^{1x}	1	4 ^{1x}	0	10 ^{2x}
at apex of heart	1	1	1	1	0	4
lower right sternal border	0	0	0	1 ^{1x}	0	1 ^{1x}
lower part both sides of sternum	0	0	0	2	0	2
upper part both sides of sternum	0	0	0	1	0	1
total	4	25 ^{3x}	13	73 ^{8x}	6 ^{1x}	121 ^{12x}

Rapid heart action

Rapid heart action as an anamnestic symptom has been described in the present material in 2 patients (no. 387 who was 2 months old at first cardiological examination, and no. 826 who was 12 months old). In both cases this palpitation or rapid heart action appears to have been constant, not of the type found in paroxysmal tachycardia (as described by Downing and Goldberg 1956, Fyler et al. 1958). Ritter et al. (1965) described 2 cases with palpitations in their material.

Voussure

Voussure occurs in the present material in not quite 35% of the infants examined for the first time before the age of 2 years. The frequency of voussure in relation to age at first examination is seen in table 11. As expected, it increases with age on examination, and is not seen during the first month of life. The incidence of voussure appears to increase both with the magnitude of the pressure in the RV or PA and with the size of the shunt (table 7 and 8, page 38), corresponding to the reports in the review of the literature. The finding by Merrild (1962) that there was a considerably greater increase in heart size in the presence of voussure than in the absence of voussure, was also confirmed in the present material, as appears from table 12.

Thrill

Thrill has been described in not quite 26% of the patients examined before the age of 2 years. As indicated in the review of the literature, thrill is found to vary with the severity of the disease. It appears to be almost constantly present in moderate to severe cases, while the reports on the incidence in the quite mild cases and in the very severe cases (including Eisenmenger's complex) vary very considerably. In the present material, there does not appear to be any definite correlation between the incidence of thrill on the one hand and the magnitude of the pressure in the RV or PA or the size of the shunt on the other hand (table 7 and 8, page 38). As mentioned by Maxwell et al. (1958), it appears to be of significance that although thrill was found in due course in all their 16 patients, it nevertheless need not be recognized before several months after birth. This also appears clearly in table 11, where the percentage occurrence of thrill increases with age (in months) at the time of the

examination. Table 13 shows the relationship between the incidence of thrill and the strength of the systolic murmur. It is seen from this that thrill is almost only recorded in murmur of degree of strength "strong" and "very strong" (= strength 5 and 6), but here too the factor mentioned presumably plays a role, as thrill may come very late after birth, and 49% of the patients in the material are less than 6 months old. It should be recalled that in the presence of the supracristal defect, the thrill is felt over the pulmonary ostium (Reynolds 1966).

The systolic murmur

The systolic murmur was found in all the patients in this material with the exception of 3 (nos. 276, 297 and 462) on the first cardiological examination. The last two patients were 1 and 2 months old, respectively, on first examination, and as mentioned by Nadas (1957), the systolic murmur need not develop before the course of the first 2-3 months, perhaps even later. The murmur was heard later - at the age of 11 months - in patient no. 276; the fact that nothing was heard on first examination cannot be due to the presence of a pressure equalization between RV and LV and the absence of a shunt, as a shunt of considerable size was demonstrated. It would rather seem to be the case that the patient conforms to the type mentioned by Nadas (1957), where the murmur may develop later than the first few months of life.

As the systolic murmur is present in almost 100% of the cases, the incidence of its presence cannot be correlated to either pressure in the RV or PA or size of shunt. 65% of the 124 infants who were examined before the age of 2 years had a strong or very strong systolic murmur, and 95% of the infants had a moderately strong or stronger murmur. In other words, only 7 infants (5%) had a weak systolic murmur (or no murmur: 3 patients), 3 of these infants were less than 2 months old at the first examination.

Table 14 shows the relationship between the strength of the systolic murmur and the localization of its maximum, in the 121 infants under the age of 2 years who had a systolic murmur at the first cardiological examination. The table shows that the typical localization for the maximum of the systolic murmur (at the lower left sternal border, as stated in the literature), is the typical localization for practically all degrees of strength of systolic murmur, and particularly so, the stronger the murmur; the next most frequent localization is "diffusely along the left sternal border". However, practically all the localizations mentioned in the literature occur, although some in only small numbers.

Table 15 shows the localization of the maximum of the murmur in relation to the magnitude of the pressure in the RV or PA, or in relation to the size of the shunt. With regard to the correlation with the pressure in the RV or PA, this is most pronounced at the low pressures, for the typical localization of the maximum of the murmur. The higher the pressure in the RV or PA, the greater the tendency for the murmur to appear in more unusual localizations. Here too the localization "diffusely along the left sternal border" is a rather frequently occurring second localization. With regard to the correlation between size of shunt and localization of the maximum of the murmur, this is of the same order of magnitude when it is a case of typical localization, for all sizes of shunt; this is also the case with the next most common localization "diffusely along the left sternal border". In other words, the more typical the localization of the maximum of the murmur, the greater the probability that the pressure is quite low in the right half of the heart, whereas this says nothing as to the size of the shunt. This finding is not quite in accordance with that of Derra et al. (1960), as these investigators found that moderately large and large defects had the murmur lying in the 2nd or 3rd left intercostal space. The 4 patients in the present material of infants under the age of 2 years at first cardiological examination, who had their maximum systolic murmur at the apex, all had large left-to-right shunts. It is thus not possible to confirm the report by Fyler et al. (1958) that a maximum systolic murmur at the apex suggests pulmonary vascular obstruction.

Table 16 shows the relationship between the maximum strength of the systolic murmur and the pressure in the RV or PA, or the size of shunt. This table shows that the stronger the murmur, the more uniformly distributed are the patients in question with respect to various pressures in RV or PA; conversely, the weaker the murmur, the more certain it is that the pressure in the RV or PA is high. Thus, considering strengths 3, 2 and 1 (as well as absence of murmur), all patients with the exception of 1 have pulmonary hypertension (in this study defined as pressure in the RV or PA $\geq$ 41 mm Hg). This does not correspond to the findings of Harned et al. (1955) and Fenig et al. (1965), who find only slight agreement between the strength of the murmur and the pressure gradient through the defect, but corresponds well to the report by Sandøe (1963). This (or another) correlation does not hold between strength of murmur and size of shunt. In other words, the weaker the systolic murmur found in a patient who is also suspected of having isolated VSD, the more likely it is that pulmonary hypertension is present, whereas nothing definite can be said as to size of shunt.

With regard to the relationship between the presence of thrill and the strength of the systolic murmur (table 13, page 44), see under "thrill".

Finally, it should be added that it has not been possible from the material to decide the duration of the systolic murmur, i. e. how large a part of the systole it has filled, nor has it been possible to determine whether the strength of the murmur has been constant as long as it was present, or whether there has been a crescendo-decrescendo murmur (Phonocardiography has not been performed).

The diastolic murmur

Table 17 shows the 12 cases in the material of infants with isolated VSD who were examined before the age of 2 years, and in whom a diastolic murmur was heard. This has therefore been found in not quite 10% of the cases, a low figure, which may perhaps be ascribed to the low age of a large part of the material. In the table, the murmur is grouped in relation to the site where it was heard at a maximum, as well as to the magnitude of the pressure in the RV or PA or the value of the shunt through the septal defect. The only patient (case no. 864) in whom the murmur was heard over the region of the pulmonary orifice (and described here as a long diastolic murmur), is a patient with pulmonary hypertension, corresponding to the description in the literature characterizing cases of "pulmonary" diastolic murmur (although the relative heart volume demonstrated radiologically is not greater than in the other patients with diastolic murmur elsewhere, and the shunt is so small that it could not be calculated on the basis of the oxygen analyses).

The 5 cases of "apical" murmur were found with moderately large, and large shunts, likewise as reported in the literature. All 5 murmurs were described as rather weak, early-diastolic and short. This does not correspond to the reports by Cleland et al. (1958), Dammann et al. (1960) and Derra et al. (1960), that short weak diastolic murmurs should be a sign of a large pulmonary vascular resistance, but on the other hand it corresponds to the descriptions by Fyler et al. (1958) and Neill and Taussig (1959) that the apical diastolic murmurs are found most frequently with large left-to-right shunts. Blount and Woodwark (1960) and Hollman et al. (1963), however, found no definite correlation between the presence of the murmur and the size of the shunt.

It is difficult to explain the third localization of the diastolic murmur at the lower left sternal border, unless in reality it is merely "apical". The 6 cases are all described as short, early-diastolic murmurs. In cases without pressure equalization it is possible that the shunt continues from the systole over into the first half of the diastole, but this explanation is not a likely one in those cases where pressure equalization is presumably present.

Table 15. Relationship between localization of the maximum of the VSD murmur and the pressure in the RV in mm Hg, or the size of the left-to-right shunt (oxygen deficit RV to RA in %), in 121 children with isolated VSD, under 2 years of age at first examination. Three of the 124 children presented no murmur.

Localization of the murmur (maximum)	Pressure in RV in mm Hg				Oxygen deficit RV to RA in %				
	0-25	26-40	41-60	≥ 61	0-9	10-14	15-19	≥ 20	total
lower left sternal border	14	17	22	29	22	21	16	23	82
upper left sternal border	1	0	1	0	1	1	0	0	2
diffusely along left sternal border	0	3	5	11	6	4	5	4	19
diffusely over entire precordium	0	0	3	7	0	4	3	3	10
at apex of heart	0	0	0	4	0	0	3	1	4
lower right sternal border	0	0	1	0	0	0	1	0	1
lower part both sides of sternum	0	0	1	1	1	0	1	0	2
upper part both sides of sternum	0	0	1	0	0	0	1	0	1
total	15	20	34	52	30	30	30	31	121

Table 16. Relationship between maximum strength of the VSD murmur and the magnitude of the pressure in the RV in mm Hg, or the size of the left-to-right shunt (oxygen deficit RV to RA in %) in 124 children with isolated VSD, who were under 2 years of age at first examination. The figures in brackets indicate the number in whom a diastolic murmur was also heard.

Pressure in RV in mm Hg	Strength of murmur						total
	No murmur	weak	moderately strong	moderately strong to strong	strong	very strong	
0-25	0	0	0	2 (0)	12 (0)	1 (0)	15
26-40	0	0	1 (0)	2 (0)	16 (2)	1 (0)	20
41-60	0	1 (0)	6 (0)	2 (0)	23 (4)	2 (1)	34
≥ 61	3 (0)	3 (0)	18 (3)	7 (0)	22 (2)	2 (0)	55
Oxygen deficit RV to RA in %							
0-9	1 (0)	1 (0)	5 (1)	6 (0)	17 (2)	1 (0)	31
10-14	0	0	7 (0)	3 (0)	19 (1)	1 (0)	30
15-19	2 (0)	2 (0)	5 (1)	2 (0)	21 (3)	0	32
≥ 20	0	1 (0)	8 (1)	2 (0)	16 (2)	4 (1)	31
total	3 (0)	4 (0)	25 (3)	13 (0)	73 (8)	6 (1)	124

Table 17. Localization of the 12 cases of diastolic murmur recorded in a total of 124 children with isolated VSD under 2 years of age at first examination, in relation to the pressure in RV or PA mm Hg, or the size of the left-to-right shunt (oxygen deficit RV to RA in %).

Localization	No.	Pressure in RV or PA			Oxygen saturation deficit RV to RA in %		
		<41 mm	41-60 mm	≥ 61 mm	0-9	10-19	≥ 20
"pulmonary"	1	0	0	1	1	0	0
"apical"	5	0	3	2	0	1	4
at lower left sternal border	6	2	2	2	2	4	0
total	12	2	5	5	3	5	4

Fig. 9. Hemoglobin values in 121 out of the 124 children with isolated VSD who were under the age of 2 years at first cardiological examination, drawn in different signatures according to pressure in the RV at first examination, together with curves for mean values of Hb and range of variation in normal children (modified from Wintrobe, 1956, so that the mean value = 100% Hb = 14.8 g% Hb).

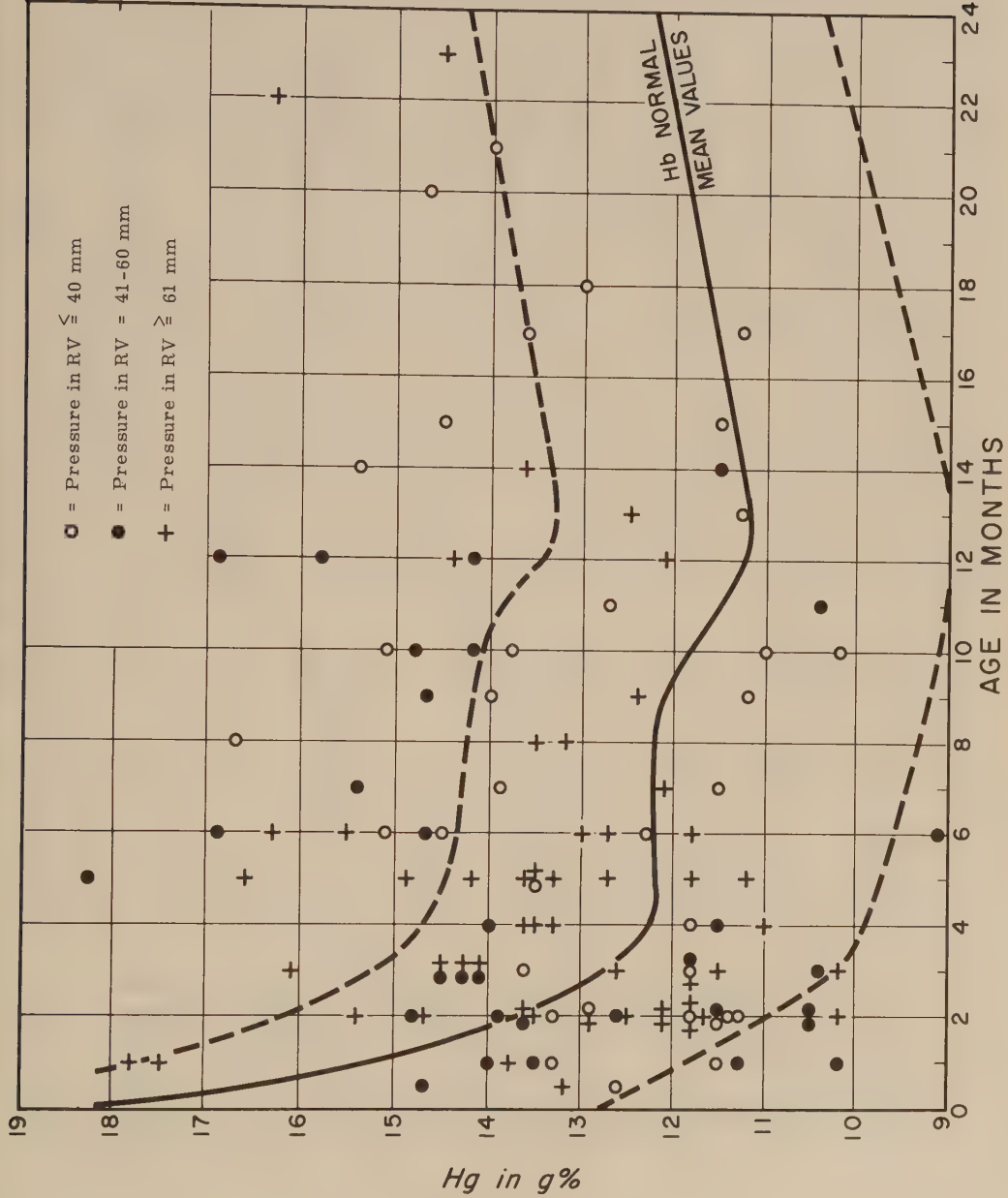
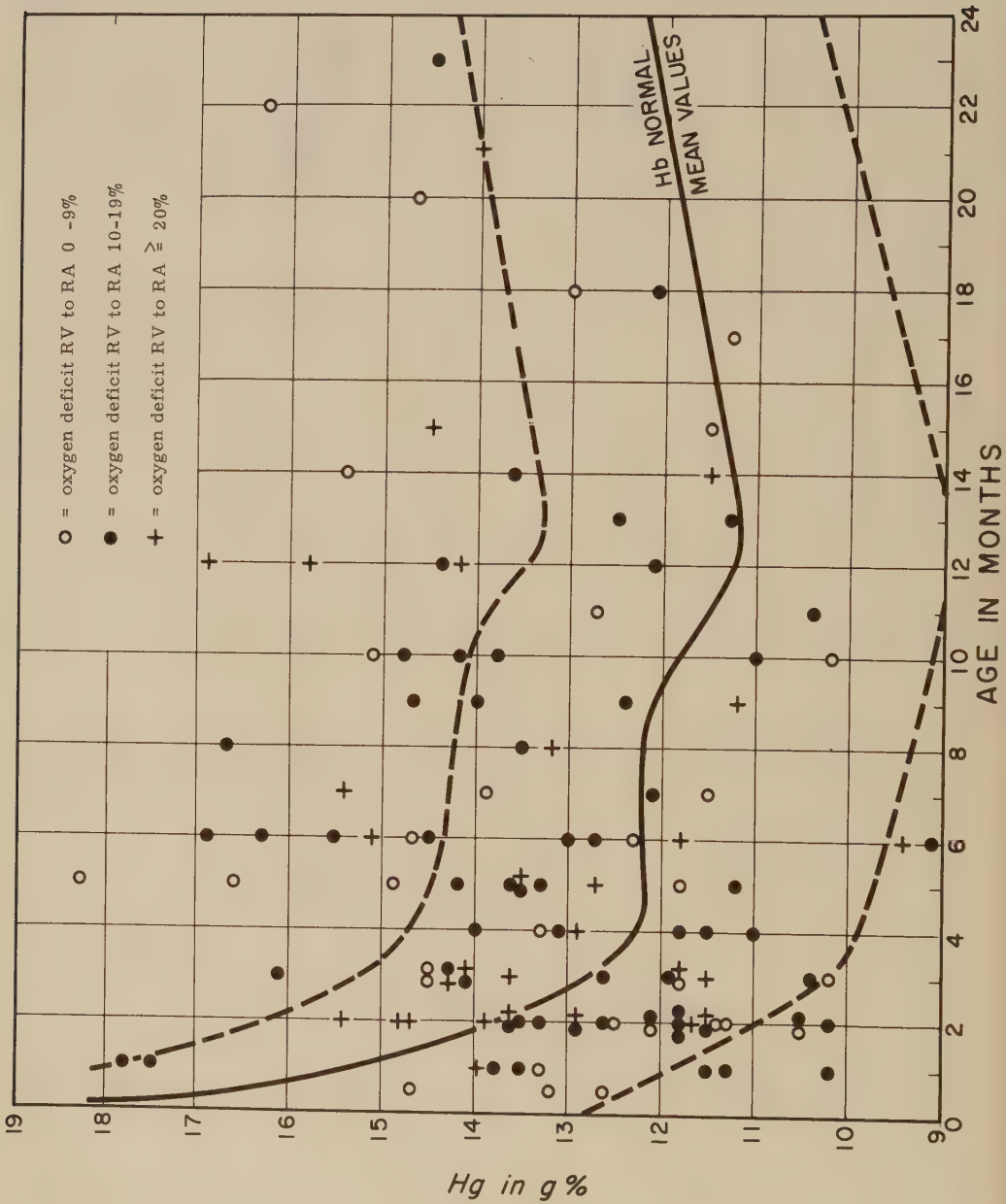


Fig. 10. Hemoglobin values in 121 out of the 124 children with isolated VSD who were under the age of 2 years at first cardiological examination, drawn in different signatures according to different sizes of shunt at first examination, together with curves for mean values of Hb and range of variation in normal children (modified from Wintrobe, 1956, so that the mean value = 100% Hb = 14.8 g% Hb).



Anemia

Of the ordinary laboratory examinations (apart from those carried out in the course of cardiac catheterization), only the hemoglobin measurements will be mentioned here, carried out in 121 out of the 124 infants under the age of 2 years at the first cardiological examination. The samples were obtained from capillary blood, and where several results were available (where there have often been considerable variations between the individual results), the test result was used which was obtained immediately prior to the cardiac catheterization. During the first few years, the results of the tests were expressed as Hb%, but in recent years as g% Hb (100% Hb = 14.8 g% Hb). Erythrocyte measurements are available from only 92 of the 124 patients, so they have not been included in the evaluation, as it cannot be anticipated that the 92 values constitute a representative selection of the 124 patients. In figs. 9 and 10, the measured Hb values have been plotted in different signatures according to the pressure in the RV or PA, or according to the various shunt sizes, to determine whether the various hemodynamic conditions had any influence on the magnitude of the various hemoglobin values. The figures also include the curves for mean values and the range of variation for various age groups of normal children (modified from Wintrobe 1956, but so that the mean value corresponds to 100% Hb = 14.8 g% Hb). It should be added that the hemoglobin values in the material appear to lie rather high in relation to the normal values, presumably because the hemoglobin measurements in the material were done on capillary blood, while normal values are determined on venous blood, and the capillary blood determinations usually lie higher than the venous blood determinations (Wintrobe 1956). From figs. 9 and 10, the hemoglobin values found do not appear to be correlated in any definite way with the corresponding hemodynamic conditions, as was found by Schaede et al. (1960). Thus, it was not possible to confirm the point of view put forward by Maxwell et al. (1958) that anemia is not unusual in isolated VSD. It appears from table 18 that lower mean Hb values were not found in infants for whom information was available on recurrent respiratory tract infections, than found in patients without these infections, in contrast to the results of Maxwell et al. (1958). In other words, the clinical finding of "anemia" is due exclusively to the strongly reduced systemic flow (cf. Dammann et al (1960)). Griffin and Essex (1951), in experimentally produced VSD in dogs, have been unable to demonstrate any significant changes in the Hb level, pre-operatively and postoperatively.

Chapter IV

Radiological examinations at first cardiological examination

General remarks on radiological examinations of the thorax in isolated VSD

The roentgenological picture of isolated VSD is above all determined by the size (and direction) of the blood flow through the defect and thereby through the lungs.

The cardiothoracic index

Since the work of Bakwin and Bakwin (1935), an evaluation of the size of the heart from a roentgenological examination (X-ray film), in an attempt to decide whether the heart has a normal size or is enlarged, has been done by measuring the cardiothoracic index (c-th index), i. e. the maximum width of the heart measured horizontally on the frontal plane film, divided by the maximum internal diameter of the thorax. This is a simple but not particularly accurate method, which, however, has found considerable application in the daily work. This measuring method was used by Taussig (1947), Engle (1954), Nadas (1957), Vickers and Kincaid (1958), Kincaid (1960), Vickers et al. (1960), Merrild (1962) and Ritter et al. (1965).

In "Nomenclature and Criteria for Diagnosis of the Heart and Blood Vessels" by The Criteria Committee of the New York Heart Ass., Inc., 5th Ed., New York 1953, it is expressly stated, however, that the c-th index should be dropped, as it is too unreliable a measure of the size of heart. Also Lind (1950) reports that the cardiothoracic index cannot be relied on.

Table 18. The mean hemoglobin value in g% in various age groups, in 121 out of 124 children with isolated VSD, under 2 years of age at first examination, in relation to the recurrence or non-recurrence of infections of the respiratory tract.

Age at first examination	No.	Mean hemoglobin value in g% in the patients			
		with recurrent respiratory tract infections		without recurrent respiratory tract infections	
		No.	Hb g%	No.	Hb g%
< 1 month	3	0		3	13, 5
1 month	9	1	13, 8	8	12, 9
2-3 months	40	5	12, 7	35	12, 7
4-5 months	18	8	12, 9	10	13, 8
6-11 months	31	14	13, 3	17	13, 3
12-17 months	14	4	13, 2	10	13, 6
18-23 months	6	3	15, 0	3	13, 3
total	121	35		86	

Volume of the heart

Determinations of the volume of the heart have been based more and more on the results in studies on large children and adults by Jonsell (1939), Liljestrand et al. (1939), Larsson and Kjellberg (1948), and on children in various age groups by Eek (1949), Kjellberg et al. (1954), Kjellberg et al. (1955) and Evans and Carpenter (1965). In the case of the youngest age groups, there are detailed studies by Lind (1950) as well as later studies by Merrild (1962), Rosendal (1966a) and Rosendal (1971).

In calculating the volume of the heart in infants on the basis of 2 roentgenograms of the thorax (one in the frontal plane and one in the sagittal plane), Lind's study (1950) is used as starting-off point, employing the formula for the volume of the ellipsoid, $\frac{4}{3}\pi \times \frac{LD}{2} \times \frac{BD}{2} \times \frac{DD}{2}$ (where LD is the long diameter, BD is the width diameter and DD is the depth diameter), multiplied by a correction factor on account of the placing of the roentgen tube near the patient. This absolute heart volume is then converted to heart volume per m^2 surface. Lind (1949) found that in a material of normal infants from 8 to 365 days old, the maximum permissible normal heart volume/ m^2 (mean value $+ 2 \times SD$) (it is only maximum value which is of interest) ranged from 285 ml/m^2 in the case of infants aged 0 days to 335 ml/m^2 in the case of infants aged 365 days (infants from 1/2-1 year), thus an increasing volume/ m^2 with increasing age, as was also mentioned by C. E. R  ih   in the discussion following Lind's work from 1949. In premature infants, the heart volume/ m^2 is less than in full-term infants. In the age group 7-14 years, Kjellberg et al. (1954) found in normal school children a maximum value of 485 ml/m^2 , from the mean value of $440 + 2 \times SD$ (from the 7th to the 14th year). (This latter study has special significance for the follow-up examination).

The recording technique employed in these 2 studies is not exactly the same as that used here, but nevertheless shows the tendency in the development of the heart volume/ m^2 surface from infant to big child, as both the studies report what the authors considered were normal values, and give in spite of everything a fair representation of how large the heart volume per m^2 surface may be, without there being a great probability that it is too large. The difference between maximum permissible heart volume/ m^2 at 7 years and 14 years of age is less than one standard deviation. (If it is permitted to interpolate to values for the maximum permissible heart volume/ m^2 from 1 year to 7 years (from Lind's study to Kjellberg et al.'s study), the value will increase by about 2 SD in this age interval, calculated from Kjellberg et al.'s study).

Pulmonary vessels

The appearance of the pulmonary vessels on the roentgenogram has been found very useful by many authors for evaluating the size of the shunt, the reaction of the pulmonary vascular system to the increased blood flow, and thereby the possibilities for operating on the condition. Highly dilated pulmonary artery, main branches of the pulmonary artery and central and peripheral branches of the artery, have been found in cases with large left-to-right shunts, while normal main branches and normal central and peripheral branches have been found in quite small left-to-right shunts. Finally, a large pulmonary artery together with large central branches, combined with small peripheral branches, have been found in cases with high pressure in the pulmonary circulation, combined with low blood flow through the pulmonary vessels, on account of high pulmonary vascular resistance, possibly so pronounced as to be a case of Eisenmenger's complex.

Right-sided aortic arch

Right-sided aortic arch has been found to occur in isolated VSD in 6% of the cases (Becu et al. 1956).

Author's material

Review

In the present study, the usual procedure for radiological examination was with the patient supported in the sitting position with lifted arms and with respectively chest and side of thorax facing the film. Oblique exposures were made following the usual practice. The distance from the roentgen tube to the film was in almost all exposures 147.5 cm, and as mentioned films were made in 4 planes with contrast in the oesophagus: frontal plane, sagittal plane, left and right oblique diameters; the films were not taken simultaneously or in any definite phase of the cardiac cycle, but as far as was possible in the phase of maximum inspiration. However, it was often difficult to take the films on account of the patients being upset and crying. If the infants were very poorly, it was impossible to expose them to too much stress, and the contrast in the oesophagus was omitted together with the two oblique views. In a few of the first patients, only one view was taken; a film in the frontal plane.

The size of the heart was evaluated from a determination of the relative

volume of the heart, since as mentioned on page 48, the cardiothoracic index is too inaccurate a method. It will therefore not be used in the present study.

Determination of the volume of the heart: in calculating the volume of the heart, the formula for the volume of an ellipsoid is used (Lind 1950, Rosendal 1966a, Rosendal 1971): $4/3\pi \times \frac{1}{2} \times \frac{b}{2} \times \frac{d}{2}$, where l, b and d are the length diameter, width diameter and depth diameter, in planes considered to pass through the center of the heart.

In making the roentgenograms, the patients have been photographed as mentioned, sitting with the chest or the side of the thorax towards the film in the two main planes (in other words slightly different from in Lind's material (1950), and the 3 diameters LD, BD and DD measured on the roentgenograms were determined as follows: LD is the length of the heart, i.e. the greatest distance from the base to the apex through the mid-point of the heart on the frontal film. BD is the distance from the transition between the pulmonary conus and the left ventricle in the left heart contour on the frontal plane view to the opposite side of the heart, at right angles to LD, i.e. BD often terminates slightly below the diaphragm (as reported by Evans and Carpenter 1965). BD does not correspond precisely to Lind's BD, but the difference is hardly of any great significance. DD is the distance from the anterior contour of the heart (or the back wall of the sternum) in the sagittal plane to the front edge of the contrast-filled oesophagus, measured horizontally at the point where the diameter is greatest. Because of the placing of the roentgen tube at a distance of 147.5 cm from the film, the actual diameters in the heart are slightly enlarged on the roentgen film, so that the values LD, BD and DD measured on the roentgenograms must be reduced by means of a correction factor K, which has been calculated under the recording conditions given as 0.46 (the figure which is used in the present study). *)

*) Calculation of the reduction factor K: LD, BD and DD are the measured values on the roentgenograms. If these values are inserted in the formula for the volume of an ellipsoid ($4/3 \pi \times \frac{LD}{2} \times \frac{BD}{2} \times \frac{DD}{2}$), too great a volume is obtained on account of the divergence of the beam. The correction is made from the formula $4/3 \pi \times \frac{1}{2} \times \frac{b}{2} \times \frac{d}{2}$, where $l = \frac{LD \times (147.5 - a)}{147.5}$ and $b = \frac{BD \times (147.5 - a)}{147.5}$, where a is the distance from the film to the imagined frontal plane in the middle of the heart), and $d = \frac{DD \times (147.5 - 1/2 \text{ th})}{147.5}$, (where 1/2 th is = 1/2 of the external thorax width at the level of the heart). From these formulae, a correction factor K_1 can be calculated (the correction factor for the diameters LD and BD on the frontal plane). This correction factor is $K_1^2 = 1 \times b \times \frac{147.5 - a^2}{147.5}$. The correction factor K_2 for the diameter DD of the sagittal plane is = $\frac{147.5 \times 1/2 \text{ th}}{147.5}$. The final correction factor K then becomes $0.523 (= \pi/6) \times K_1 \times K_2 = 0.46$ (approximate value).

This correction factor is not quite constant from patient to patient, and falls slowly with increasing age to about 0.42 in adults (Jonsell 1939), but within the age range covered by the present study, which also holds for the follow-up material, the use of a fixed correction factor (= 0.46) will give such a small error that it can be ignored (Rosendal: personal communication, 1966b). This holds all the more when we take into consideration that there are certain unavoidable measuring errors in the calculation of the volume, the measurements of the various diameters on the roentgenogram involving an uncertainty of a few millimeters, that the diameter of the heart depends on the cycle of the heart, that the anteroposterior diameter of the thorax varies with the phase of the respiration, and that the size of the thorax in these slightly built infants with heart disease will vary less between the various age groups than between normal, healthy infants (see Evans and Carpenter 1965).

The calculated volume was then used to calculate the relative volume of the heart, i. e. the volume per m^2 surface in the infant, using DuBois' surface nomogram, from the values for the infant's weight and length.

In addition to the general evaluation of the size of the heart, got with the help of heart volume/ m^2 , an attempt was made to evaluate the size of the individual chambers in relation to those of the normal heart, on the lines laid down by the Criteria Committee of the New York Ass. (1953).

The pulmonary vessels were evaluated as indicated in the literature: normal vascular conditions, various degrees of expansion of the pulmonary vessels, and reduced vascular density in the lungs. An attempt was also made to demonstrate possible cases with particularly wide central pulmonary vessels and narrow peripheral pulmonary vessels.

Table 19 is a record of all information which has been obtained from the roentgenograms on heart and the vascular conditions in the lungs for each separate patient, together with their age, the systolic pressure in RV or PA in mm Hg, and the size of the left-to-right shunt expressed by the oxygen saturation deficit, RV to RA in % (in addition, the results are included from the follow-up examination for use later in the study). The separate problems will now be discussed.

Volume of the heart

The relative volume of the heart, i. e. the absolute volume expressed per m^2 surface of the patient, a value which as mentioned must be expected to give the best indication of the true size of the heart, has been shown in table 20 as well as in table 19 (in relation to the pressure in RV or PA and the size of the left-

Table 19. This table shows the individual findings on radiological examination of the thorax in 144 children with isolated VSD, 124 of whom were under 2 years of age at first cardiological examination, together with the findings at follow-up examination.

Abbreviations and signatures: "No." is the examination number of the patient. When the number is underlined, this signifies that the patient underwent a palliative operation after the first cardiological examination. "Pressure/Shunt" are the values measured at first cardiological examination for pressure in RV in mm Hg and size of left-to-right shunt expressed as oxygen deficit RV to RA in %. Rel. heart vol. = abs. heart vol. / m^2 body surface of patient. The value of abs. heart vol. is in ml. The size of the individual heart chambers is indicated by the following signs: 0 = normal, (+) = slightly enlarged, + = enlarged, ? = cannot be evaluated. The pulmonary conus is evaluated as follows: - = concave, 0 = normal, prom. = prominent, n.c.d. = normal contour disappeared (normal pulmonary arterial segment contour disappeared). Pulmonary vasculature is evaluated as follows: 0 = normal, (+) = slightly increased, + = increased, ++ = strongly increased. "Yrs. 1st exam. - f.u." = number of years from first cardiological examination to follow-up examination.

Data from first examination

[illegible]

No.	Age in yrs.	Pressure Shunt	Rel. heart vol.	Size of individual heart chambers RA LA RV LV	Pulm- onary conus	Yrs. 1st exam. - f.u.	Age in yrs.	Rel. heart vol.	Size of heart chambers RA LA RV LV	Pulm- onary conus	Pulm- onary vasc.
<u>2</u>	2/12	79/12	565	+	+	+	?	+	+	+	+
<u>4</u>	5/12	59/9	-	+	+	+	prom.	++	dead	++	+
<u>5</u>	5/12	81/45	-	+	+	+	n. c. d.	++	dead	++	+
<u>10</u>	18/12	52/13	-	+	?	+	prom.	(+)	dead	(+)	+
<u>16</u>	3/12	70/10	-	+	?	+	n. c. d.	++	7 5/12	7 8/12	420
<u>17</u>	10/12	44/14	-	+	+	+	prom.	++	7 1/12	7 11/12	520
<u>20</u>	10/12	19/10	-	+	+	+	o	(+)	7 1/12	7 11/12	360
<u>23</u>	3/12	66/8	-	+	+	+	n. c. d.	+	7 3/12	7 6/12	555
<u>29</u>	2/12	76/33	975	+	?	+	prom.	(+)	7 2/12	7 4/12	875
<u>35</u>	2/12	92/12	-	+	?	+	o	+	dead		
<u>37</u>	14/12	49/32	-	+	?	+	prom.	+	6 9/12	7 11/12	515
<u>47</u>	3/12	56/14	-	(+)	+	+	o	++	5 10/12	6 1/12	465
<u>49</u>	9/12	36/20	-	+	?	+	o	o	6 7/12	7 4/12	390
<u>58</u>	4/12	74/52	-	+	?	+	prom.	(+)	6 9/12	7 1/12	540
<u>68</u>	4/12	61/6	-	+	?	+	o	+	7 1/12	7 5/12	460
<u>83</u>	2/12	70/15	505	+	?	+	prom.	+	dead		
<u>86</u>	14/12	25/2	375	+	+	+	o	o	6 3/12	7 5/12	460
<u>88</u>	2/12	76/59	-	+	?	+	prom.	++	dead		
<u>98</u>	6/12	67/30	725	+	+	+	o	+	dead		
<u>102</u>	6/12	30/43	-	+	+	+	o	++	5 10/12	6 4/12	370
<u>103</u>	9/12	81/19	580	+	+	+	o	+	5 10/12	6 7/12	675
<u>111</u>	7/12	60/31	470	+	+	+	(prom.)	++	5 9/12	6 4/12	425
<u>119</u>	12/12	41/28	360	+	+	+	n. c. d.	+	5 7/12	6 7/12	365

Table 19.

Data from first examination					Data from follow-up examination							
No.	Age in yrs.	Pressure Shunt	Rel. heart vol.	Size of individual heart chambers RA LA RV LV	Pulm-onary conus	Pulm-onary vasc.	Yrs. 1st exam. - f. u.	Age in yrs.	Rel. heart vol.	Size of individual heart chambers RA LA RV LV	Pulm-onary conus	Pulm-onary vasc.
146	2/12	43/29	405	+ + + +	+ n. c. d.	(+)	4 7/12	4 9/12	520 (+)	o (+)	o	(+)
170	6 9/12	33/12	455	+ o + +	+ prom.	+	5 9/12	12 6/12	555 +	o + +	prom.	+
178	3	27/4	330	+ ? + +	o	(+)	5 2/12	8 2/12	370 o	o o o	o	o
189	6/12	29/19	-	+ o + +	o	o	dead					
191	3/12	24/21	285	o o o o	o	o	4 11/12	5 2/12	290 o	o o o	o	+
207	12/12	66/11	500	+ o o o	o	+	dead					
214	7	94/11	470	o o + o	+ prom.	(+)	4 7/12	11 7/12	495 o	o + (+)	n. c. d.	(+)
224	2/12	20/12	315	o o o o	o	o	4 5/12	4 7/12	350 o	o o o	o	o
236	8/12	71/21	695	+ + + +	o	++	4 6/12	5 2/12	410 (+)	? + +	o	+
238	10/12	43/16	-	+ + + +	o	+	4 3/12	5 1/12	380 o	o (+)	o	(+)
244	10	48/17	870	+ o + +	+ prom.	++	4 6/12	14 6/12	1095 +	+ + +	n. c. d.	++
247	18/12	70/18	635	+ + + +	+ n. c. d.	+	dead					
250	5/12	26/19	365	(+) o o o	+ n. c. d.	(+)	4 7/12	5	435 (+)	o o o	(prom.)	o
262	2/12	76/25	675	+ + + +	o	+	dead					
268	6/12	68/18	635	+ + + +	+ prom.	++	4 4/12	4 10/12	430 +	o o o	n. c. d.	(+)
269	5/12	80/7	500	+ + + +	+ prom.	++	4 5/12	4 10/12	500 +	o o o	prom.	(+)
272	7/12	27/8	385	+ o o o	o	(+)	4 3/12	4 10/12	760 +	o + +	prom.	+
273	3 9/12	85/21	965	+ + + +	+ prom.	++	dead					
276	6/12	82/15	470	+ o o o	o	+	4 5/12	4 11/12	410 +	o + o	o	o
277	13/12	86/15	475	+ + + +	o	+	4 3/12	5 4/12	415 (+)	o + +	o	+
289	2 9/12	26/10	600	+ + + +	+ prom.	(+)	not followed up					
290	15/12	16/20	285	o o o o	o n. c. d.	+	3 11/12	5 2/12	375 o	o o o	o	(+)
291	3/12	48/8	445	+ o + +	? (+)	o	6 3/12	6 6/12	425 +	o + +	n. c. d.	(+)

Table 19

Data from first examination

No.	Age in yrs.	Pressure Shunt	Rel. heart vol.	Size of individual heart chambers				Pulm- onary vasc.
				RA	LA	RV	LV	
292	15/12	16/7	260	o	o	o	(+)	o
297	1/12	80/16	330	+	o	+	+	(+)
298	4/12	26/10	440	+	o	+	+	+
299	5/12	69/11	420	+	+	+	+	n. c. d.
323	2/12	70/19	505	+	+	+	+	prom.
324	6	35/7	775	(+)	(+)	+	+	prom.
334	22/12	79/8	370	+	+	+	+	+
335	5/12	68/8	410	+	+	+	+	++
338	3/12	80/37	430	+	+	(+)	(+)	?
353	1/12	57/27	705	+	+	+	+	+
371	2/12	57/13	525	+	+	+	+	++
379	10/12	59/37	-	+	o	+	+	prom.
381	5/12	71/24	515	+	+	+	+	n. c. d.
384	2/12	45/13	415	+	o	o	o	o
387	2/12	38/12	500	+	+	+	+	prom.
401	12/12	77/17	465	+	+	+	+	n. c. d.
403	2	8/12	62/16	+	+	+	+	prom.
407	7/12	67/18	435	+	+	+	+	+
408	10/12	33/5	300	o	o	o	o	+
414	3/12	75/13	340	+	o	+	+	+
415	5	2/12	29/5	390	(+)	o	(+)	n. c. d.
416	2	1/12	80/24	660	+	+	+	prom.
422	3/12	68/13	480	+	o	+	+	?
424	2/10/12	40/16	375	(+)	o	o	o	prom.

Data from follow-up examination

Yrs. 1st exam. - f. u.	Age in yrs.	Rel. heart vol.	Size of individual heart chambers				Pulm- onary vasc.
			RA	LA	RV	LV	
4	5	3/12	320	(+)	o	(+)	o
dead							(+)
3	11/12	4	3/12	435	+	o	(+)
dead							n. c. d.
3	11/12	4	1/12	490	+	o	+
2	11/12	8	11/12	690	(+)	+	+
3	6/12	5	5/12	360	o	o	o
dead							prom.
dead							+
3	7/12	3	8/12	400	+	+	(+)
3	5/12	3	7/12	575	+	+	+
dead							n. c. d.
3	10/12	4	3/12	525	+	o	+
2	11/12	3	1/12	400	o	o	+
3	1/12	3	3/12	465	+	o	o
3	6/12	4	6/12	725	+	+	+
2	11/12	5	7/12	435	+	o	+
3	3	3	7/12	540	+	+	+
3	3/12	4	1/12	295	o	o	o
3	2/12	3	5/12	465	o	(+)	+
3	4/12	8	6/12	510	o	o	+
2	10/12	4	11/12	810	+	+	+
3	4/12	3	7/12	500	+	+	+
2	2/12	5		420	o	o	+

Table 19.

Data from first examination

No.	Age in yrs.	Pressure		Rel. heart vol.	Size of individual heart chambers				Pulm- onary conus	Pulm- onary vasc.	Yrs. 1st exam. - f.u.	Age in yrs.	Rel. heart vol.	Size of individual heart chambers				Pulm- onary conus	Pulm- onary vasc.	
		Shunt			RA	LA	RV	LV						RA	LA	RV	LV			
425	17/12	34/20	540	(+)	o	o	(+)	o	+	3	3/12	4	8/12	540	(+)	o	o	(+)	prom.	(+)
430	6/12	25/8	285	o	o	o	o	o	o	3	4/12	3	10/12	325	o	o	o	o	o	o
446	6/12	74/30	660	+	+	+	+	(prom.)	+	2	7/12	3	1/12	635	+	+	+	+	prom.	++
456	3/12	64/23	450	+	+	+	+	o	+	3	10/12	4	1/12	590	o	o	+	+	o	+
462	2/12	71/9	535	+	+	+	+	n. c. d.	++	dead										
463	10	1/12	31/0	275	o	o	(+)	o	o	2	8/12	12	9/12	330	o	o	o	o	o	o
465	7	2/12	13/3	400	o	o	o	o	o	2	7/12	9	9/12	445	(+)	o	o	o	o	(+)
467	<1/12	65/6	310	+	+	+	o	o	+	dead										
475	3/12	47/13	370	(+)	o	(+)	(+)	o	+	2	2/12	2	5/12	380	o	o	(+)	(+)	o	+
476	21/12	28/21	470	+	o	+	+	(prom.)	(+)	2	10/12	4	7/12	500	o	o	o	(+)	n. c. d.	(+)
477	1/12	29/12	340	(+)	o	+	+	o	(+)	2	11/12	3		490	+	o	+	+	o	(+)
479	6/12	54/7	275	+	o	+	o	o	o	2	11/12	3	5/12	350	o	o	o	o	o	o
496	11/12	19/9	375	(+)	o	o	o	o	o	1	8/12	2	7/12	365	o	o	o	o	n. c. d.	o
506	10/12	36/6	555	+	o	+	+	prom.	+	2	2/12	3		555	+	o	+	+	prom.	+
518	2/12	56/28	580	+	+	+	+	o	+	2		2	2/12	535	+	+	+	o	o	o
522	12/12	49/21	490	+	+	+	(+)	o	+	2	4/12	3	4/12	440	(+)	o	(+)	(+)	o	(+)
542	4/12	56/15	565	+	+	+	+	prom.	+	2	2/12	2	6/12	565	(+)	o	(+)	+	n. c. d.	o
547	2/12	48/20	435	+	+	+	(+)	o	+	dead										
550	2/12	41/21	420	+	+	+	(+)	n. c. d.	+	2	9/12	2	11/12	485	+	(+)	+	(+)	prom.	(+)
554	8	8/12	23/0	335	o	o	o	o	o	2		10	8/12	395	o	o	o	o	o	o
555	8/12	27/13	440	+	o	(+)	(+)	n. c. d.	+	2	1/12	2	9/12	-	o	o	(+)	o	o	+
556	5/12	72/16	425	+	+	+	+	n. c. d.	+	1	10/12	2	3/12	455	+	o	+	+	n. c. d.	+
561	2/12	63/15	455	+	+	+	+	n. c. d.	++	2		2	2/12	610	+	+	+	+	o	+
564	2/12	71/16	400	+	+	+	+	?	(+)	2		2	2/12	305	o	o	+	+	(prom.)	+

Table 19.

Data from first examination				Data from follow-up examination												
No.	Age in yrs.	Pressure Shunt	Rel. heart vol.	Size of individual heart chambers			Pulmonary conus	Pulmonary vasc.	Yrs. 1st exam. - f. u.	Age in yrs.	Rel. heart chambers vol.			Pulmonary conus	Pulmonary vasc.	
				RA	LA	RV					LA	RV	LV			
571	6/12	78/18	520	+	+	(+)	(prom.)	+	2 3/12	2 9/12	505	+	o	(+)	o	+
572	3/12	66/22	435	+	+	+	(prom.)	+	1 11/12	2 2/12	390	o	o	o	+	n. c. d. (+)
584	10/12	38/17	285	+	o	+	(prom.)	+	3	3 10/12	410	o	o	(+)	+	(prom.) (+)
In the following patients, data are available for the first examination only, no follow-up was performed.																
597	6/12	46/17	295	+	o	o	o	(+)								
599	11 10/12	24/10	460	o	o	o	o									
603	1/12	58/19	235	o	o	+	(prom.)	(+)								
607	21/12	21/8	250	(+)	o	o	(+)	o								
618	3/12	42/19	220	o	o	o	o	+								
624	1/12	66/13	365	(+)	o	(+)	+	prom.	+							
630	7/12	23/5	260	o	o	o	o	o								
635	2/12	22/14	250	o	o	o	(+)	o								
641	2/12	32/9	175	o	o	o	?	o								
647	2/12	25/18	475	o	o	+	prom.	o								
651	1/12	54/15	275	o	o	o	o	(+)								
660	6 6/12	30/14	410	+	o	o	n. c. d.	+								
678	3/12	80/30	410	+	+	+	?	+								
682	5 29/6	460	o	o	o	o	(+)	(+)								
686	3/12	21/5	320	o	o	o	?	(+)								
689	14/12	79/18	500	+	+	+	+	+								
690	2 8/12	20/0	295	o	o	o	o	o								
700	11/12	45/17	515	+	+	+	?	(+)								
710	4/12	44/16	500	+	+	+	(+)	+								
711	18/12	33/8	435	+	o	+	(prom.)	o								

Table 19.

Data from first examination

No.	Age in yrs.	Pressure Shunt	Rel. heart vol.	Size of individual heart chambers				Pulm- onary conus	Pulm- onary vasc.
				RA	LA	RV	LV		
716	8/12	65/10	525	+	+	+	o	prom.	(+)
719	3/12	62/6	480	+	o	o	o	n. c. d.	(+)
721	2/12	39/6	315	o	o	o	o	o	o
722	<1/12	28/5	355	o	o	o	o	n. c. d.	o
724	2	26/1	325	o	o	o	o	o	o
726	4	87/13	570	+	+	+	+	prom.	++
<u>727</u>	2/12	66/30	415	+	+	o	o	(prom.)	+
<u>728</u>	4/12	85/18	435	+	+	+	+	o	+
730	13/12	33/17	390	o	(+)	o	o	o	+
745	1/12	47/14	405	+	+	+	+	?	+
747	23/12	79/14	515	+	+	+	+	prom.	+
755	17/12	24/9	330	o	o	+	+	?	(+)
759	5/12	82/13	380	+	+	+	o	?	+
764	9/12	51/13	360	+	+	+	o	o	+
<u>787</u>	6/12	79/12	-	+	+	+	+	?	+
789	4/12	72/17	395	+	+	+	+	?	++
794	9/12	40/11	245	o	o	o	o	o	o
807	2/12	44/8	400	+	o	+	o	o	+
815	1/12	24/8	275	o	o	o	o	?	(+)
822	6/12	49/19	585	+	+	+	+	o	+
826	12/12	58/21	610	+	+	+	+	o	+
848	5/12	61/14	490	+	+	+	+	o	+
855	<1/12	50/6	385	(+)	o	o	o	o	o
<u>858</u>	5/12	69/9	370	+	(+)	+	(+)	n. c. d.	++
<u>864</u>	2/12	78/0	505	+	+	+	+	o	++
<u>871</u>	1/12	63/16	380	+	o	+	(+)	o	+
<u>873</u>	3/12	60/13	595	+	+	+	o	o	+

Table 20. Heart vol./m² body surface in 125 out of 144 children with isolated VSD, 105 of them (out of 124) under the age of 2 years at first cardiological examination, in relation to the left-to-right shunt (expressed by the oxygen deficit RV to RA in %), and to the pressure in the RV or PA. The figures in brackets indicate the number of patients undergoing operation immediately after this examination.

Vol/m ² in ml	Number total <2 yrs		Size of shunt							
			0 - 9%		10 - 14%		15 - 19%		≥ 20%	
	total	<2 yrs	total	<2 yrs	total	<2 yrs	total	<2 yrs	total	<2 yrs
≤ 299	18	16	9	7	2	2	5	5	2	2
300-399	33	27	17(1)	13(1)	7	7	8(1)	6(1)	1	1
400-499	37	31	6(1)	4(1)	11(1)	7(1)	9(3)	9(3)	11(5)	11(5)
500-599	24	22	4(2)	4(2)	9(4)	7(4)	8(4)	8(4)	3(2)	3(2)
600-699	7	6	0	0	0	0	2(2)	2(2)	5	4
≥ 700	6	3	1	0	0	0	1	0	4(3)	3(2)
total	125	105	37	28	29	23	33	30	26	24

Vol/m ² in ml	Number total <2 yrs		Pressure in RV or PA in mm Hg							
			0 - 25 mm		26 - 40 mm		41 - 60 mm		≥ 61 mm	
	total	<2 yrs	total	<2 yrs	total	<2 yrs	total	<2 yrs	total	<2 yrs
≤ 299	18	16	9	8	4	3	5	5	0	0
300-399	33	27	6	5	11	7	5	5	11(2)	10(2)
400-499	37	31	3	1	7	4	8(1)	8(1)	19(9)	18(9)
500-599	24	22	0	0	4	3	7(4)	7(4)	13(8)	12(8)
600-699	7	6	0	0	0	0	1	1	6(2)	5(2)
≥ 700	6	3	0	0	1	0	2(1)	1(1)	3(2)	2(1)
total	125	105	18	14	27	17	28	27	52	47

to-right shunt). The relative volume of the heart is rather well correlated with the pressure in RV or PA but not in general with the size of the shunt (Sandøe 1963 found considerable heart enlargement correlated both with pressure in RV and left-to-right shunt expressed as flow-ratio). As mentioned in the clinical section, the most severe clinical symptoms have rather a good correlation with the pressure in the right half of the heart, but only to a lesser degree with the size of the left-to-right shunt. The determination of the relative volume of the heart has thus a certain significance, as it may be accepted that the greater the heart volumes/m² that can be demonstrated, the more severe is the disease picture, taken with a certain reservation.

Using the normal values given on page 49 for the heart volume per m² surface of the healthy infant (the normal upper limit = the mean value + 2 × the standard deviation), we find that only 7 out of 105 infants under the age of 2 years with isolated VSD had a normal heart size (of these, 6 had a pressure in the RV or PA $\bar{<}$ 40 mm Hg and one had a pressure = 41-60 mm Hg in the RV or PA).

Size of the heart chambers

In tables 21 and 22, the question has been examined whether there is any correlation between the estimated size of the left atrium (LA) and the left ventricle (LV), evaluated on the basis of the roentgenograms and pressure in the RV or PA, or on the size of the left-to-right shunt. It is seen that in the case of both chambers, there is more or less a correlation between the size of chamber (LA and LV) and the value of the pressure in the RV or PA: the lower the pressure, the more frequently are the chambers evaluated as normal; the greater the pressure, the greater the number of enlarged chambers found in the material. The same tendency also holds with regard to the relation of the chambers to the size of the shunt.

Pulmonary vessels

The density of the pulmonary vasculature is shown in table 19 page 52 and in table 23. As table 23 shows, there appears to be a quite good correlation between the systolic pressure in RV or PA, or the size of the left-to-right shunt, and the degree of density of the pulmonary vasculature, as well as between the relative volume of the heart and the degree of density of the pulmonary vasculature, as also found by Sandøe (1963). In addition, an examination was made in

each case to establish whether it was possible to demonstrate individual patients with strikingly wide central pulmonary vessels and weakly pronounced peripheral pulmonary vessels (see page 52). This was only demonstrated with certainty in one case at the first cardiological examination: patient no. 764 A.K. (but this patient did not come to the follow-up examination). *)

Kerley lines could not be demonstrated in any one case.

The region of the pulmonary conus

In table 24, the question has been examined whether any correlation exists between the appearance of the pulmonary conus region and the magnitude of the pressure in the RV or PA, or the size of the left-to-right shunt. As the table shows, there is some tendency to enlargement of the region of the pulmonary conus with increasing pressure, just as there is some correlation between the size of the pulmonary conus and the size of the left-to-right shunt. A high pressure in RV or PA tends to expansion of the pulmonary conus (disappearance of the normal pulmonary arterial segment contour increasing to prominence of the pulmonary conus), just as this is the case with increasing left-to-right shunt, as also found by Sandøe (1963).

Right aortic arch

Right aortic arch was found in 8 cases, i. e. 5.5%, corresponding to the figure found in the literature (Becu et al. 1956, 6%).

*) This condition has also been demonstrated in a further case on follow-up examination: patient No. 550 J.E.P., in whom it was not found at first examination. This patient has undoubtedly pulmonary hypertension of the progressive type, with a rise in the measured systolic pressure in RV from first examination to follow-up examination of 41 mm Hg to 100 mm Hg. These conditions have also been demonstrated, although with less certainty, in two patients, No. 277 P.K.H. and No. 334 K.S., in the first at follow-up examination, in the second only at first examination, but not with certainty at follow-up examination, in spite of the fact that both were cyanotic at follow-up examination, and must be considered to have developed into cases of Eisenmenger syndrome (see page 124 under "Follow-up examination").

Table 21. Size of left atrium (LA), evaluated on the basis of roentgenograms of the heart in 124 children with isolated VSD, under 2 years of age at first examination, in relation to the pressure in RV or PA, and to the size of the left-to-right shunt. In almost all cases the roentgenograms were taken in 4 projections and with contrast in the oesophagus.

Pressure in RV or PA in mm Hg	Size of left atrium		could not be evaluated	total
	"normal"	"slightly enlarged" + "enlarged"		
0-40	31	3	1	35
41-60	13	19	2	34
≥ 61	11	37	7	55
total	55	59	10	124

Oxygen deficit
RV to RA in %

0-9	23	7	1	31
10-19	26	32	4	62
≥ 20	6	20	5	31
total	55	59	10	124

Table 22. Size of left ventricle (LV), evaluated on the basis of roentgenograms of the heart in 124 children with isolated VSD, under 2 years of age at first examination, in relation to the pressure in RV og PA, and to the size of the left-to-right shunt. In almost all cases the roentgenograms were taken in 4 projections and with contrast in the oesophagus.

Size of left ventricle

Pressure in RV or PA in mm Hg	"normal" total	"slightly enlarged" total	"enlarged" total	total
0-40	21	5	9	35
41-60	10	7	17	34
≥ 61	10	5	40	55
total	41	17	66	124

Oxygen deficit RV to RA in %				
0-9	19	5	7	31
10-19	18	7	37	62
≥ 20	4	5	22	31
total	41	17	66	124

Table 23. Density of pulmonary vasculature in 124 children with isolated VSD, under 2 years of age at first examination, in relation to pressure in RV og PA, and to the size of the left-to-right shunt expressed by the oxygen deficit RV to RA in %, and further in relation to heart volume/m² body surface. In the last case, only 105 of the 124 children are represented, as the volume determination could not be performed in the remainder due to lack of a lateral view.

Density of pulmonary vasculature

Pressure in RV og PA in mm Hg	normal = 0	sl. increased = (+)	increased = +	much increased = ++	total
0-40	18	8	7	2	35
41-60	4	6	18	6	34
$\geq$ 61	0	7	35	13	55
total	22	21	60	21	124

Oxygen deficit RV to RA in %					
0-9	14	5	6	6	31
10-19	6	12	35	9	62
$\geq$ 20	2	4	19	6	31
total	22	21	60	21	124

Heart volume/m ² in ml					
$\leq$ 299	9	4	3	0	16
300-399	7	7	11	2	27
400-499	4	4	19	4	31
$\geq$ 500	0	3	21	7	31
total	20	18	54	13	105

Table 24. Appearance of the pulmonary conus region on frontal film of thorax in 124 children with isolated VSD, under 2 years of age at first examination, in relation to pressure in the RV or PA, and to the size of the left-to-right shunt (expressed by the oxygen deficit from RV to RA in %).

Pressure in RV or PA in mm Hg	Appearance of pulmonary conus					total
	concave	normal	normal contour disappeared	pulmonary conus prominent	?	
0-40	0	22	4	6	5	37
41-60	0	18	3	8	5	34
≥ 61	0	19	12	14	8	53
total	0	59	19	28	18	124

Oxygen deficit RV to RA in %						
0-9	0	17	5	4	5	31
10-19	0	30	8	14	10	62
≥ 20	0	12	6	10	3	31
total	0	59	19	28	18	124

Final remarks

The radiological examination has been of importance for evaluating the size of the whole heart in determining the volume of the heart/ m^2 surface, for evaluating the size of the individual heart chambers, and also, indirectly, for evaluating the hemodynamic conditions in the heart, where the volume of the heart/ m^2 surface is quite well correlated with the pressure in the right half of the heart, but only to a slight degree with the size of the left-to-right shunt. Especially in the case of the left atrium and the left ventricle, it has been possible to demonstrate a greater or lesser correlation with the pressure in the RV or PA, but here too with the size of the left-to-right shunt. It is found that the size of LA and LV is determined both by pressure in RV or PA and by the size of the left-to-right shunt. It must therefore be assumed that it is also the contribution of the left ventricle to the high pulmonary pressure which has the effect of enlarging the LV, and that secondarily an enlargement of the left atrium also develops, on account of the increased diastolic volume of the left ventricle, with an increased inflow pressure as a result of this.

The density of the pulmonary vasculature could be shown to be rather well correlated with both pressure in RV or PA, and with the size of the shunt. With regard to the appearance of the region of the pulmonary conus, a certain correlation has been shown between the size of this (expansion) and on the other hand the pressure in the RV or PA and the size of the shunt.

Chapter V

Electrocardiographic investigations

The electrocardiogram provides an important support in the diagnosis of isolated VSD, and in evaluating the hemodynamic relationships in the disease.

Review of the literature

ECG in isolated VSD in children

Most of those authors who discuss the significance of the ECG in isolated VSD in infants, emphasize this investigation (with the exception of Taussig 1947 and Downing and Goldberg 1956, who find that it has slight value and that any possible deviations are non-specific for VSD).

More or less generally, it may be said that conditions with small VSD without any demonstrable left-to-right shunt or with only a small left-to-right shunt, and with a normal pressure in RV or PA, most often show a normal ECG. However, it is possible to observe signs of a slight left ventricular hypertrophy from the precordial leads. With increased left-to-right flow (large defects), but slight pulmonary vascular resistance, left ventricular hypertrophy is most often seen. With large VSD and high pressure in RV or PA, increasing to pressure equalization in the ventricles, either a purely right ventricular hypertrophy is seen (when the flow through the lungs is very small either because of strong pulmonary vascular resistance or because of the development of hypertrophy of the crista supraventricularis in the outflow tract of the RV), or right + left = combined ventricular hypertrophy, when some flow is maintained through the pulmonary circulation as the result of rather low pulmonary vascular resistance. The right ventricular hypertrophy found is most often of moderate degree (as in Fallot's tetralogy), with high RV_1 and

RV₂. The QRS complex is of types rR, Rs, R, rsR, qR or Rr, with possibly deep waves over the left precordium; in addition, positive, diphasic or inverted TV₁ and TV₂. Abnormally tall PV₁ suggests pronounced right atrial hypertrophy. Likewise, left ventricular hypertrophy is moderate with tall RV₆ (and RV₅), deep QV₆ (and QV₅) and very tall pointed TV₆ (and TV₅), or sometimes deep SV₁ and SV₂. The QRS complexes are often of types qRs or qRS with a positive T wave.

QRS complexes with tall diphasic amplitude are seen in many cases, both in the standard leads as well as over the right and middle precordium, and are reckoned to be an expression of the biventricular hypertrophy which is most often seen in VSD, originally described by Katz and Wachtel (1937) as a non-specific sign in standard limb leads in congenital heart disease, but later by Burchell (1949), Blount et al. (1955), Marsico et al. (1955), Hubbard and Angle (1957), Sodi-Pallares et al. (1958), Char et al. (1959), Toscano-Barboza and DuShane (1959), Warren and Jannicelli (1959) and Burch and De Pasquale (1960) in the precordial leads as frequently occurring in VSD. With regard to the electric axis of the heart, in mild cases this is most often normal or slightly left-deviating, while the combination: left axis deviation + right ventricular hypertrophy is rare. In pronounced pulmonary hypertension, however, there is almost always right axis deviation, and as reported by Keith (1966), the electric axis together with other data provide a good indication of the condition in the lung vessels and the magnitude of the pulmonary vascular resistance. There may be signs of enlargement of the atria - or possibly only one of them - with an increase in the height and duration of the P waves. The P-Q or the P-R interval is most often normal, but may be prolonged. Incomplete right branch block is seen (but more rarely than in ASD). Splitting of the QRS in the right precordial leads, as expressing complete branch block, has been described both in mild and severe cases of isolated VSD. An M-shaped QRS (as a sign of complete branch block) is more frequent in severe cases of isolated VSD with pulmonary hypertension than in mild cases. Incomplete a-v block may be seen. Complete a-v block may also be seen in VSD, but is very uncommon and is only seen in cases with severe pulmonary hypertension (for literature and references see Maranhao et al. 1965). It should be pointed out here, however, that the criteria employed by the various authors mentioned for right, left and combined ventricular hypertrophy are not quite identical, or the same as the criteria used in the present study (which are those given by Keith et al. 1958).

Vince and Keith (1961) find the ECG valuable for determining the degree of severity of the hemodynamic conditions. With regard to the flow through the defect, this is found to be low if the ECG is normal; if the ECG shows signs

of left hypertrophy, the flow is usually not so great, but occasionally increases to more than 4 times the systemic flow. If the ECG showed exclusively signs of right hypertrophy, the pulmonary blood flow was not very great. The greatest blood flow and the greatest variations in the size of the blood flow were found in those cases where the ECG showed combined hypertrophy and a large QV_6 . The authors also found some correlation between pressure in RV and ECG. With a normal ECG, the pressure in RV was rarely above 40 mm Hg; if there was left ventricular hypertrophy, most of the patients had a pressure in the RV less than 50 mm Hg. Also here, that group with combined ventricular hypertrophy showed the greatest variation. If the ECG showed a purely right ventricular hypertrophy, the pressure in the RV was rarely below 60 mm Hg and almost always of the same magnitude as the systemic pressure.

Finally, it should be added that the emphasis is on including studies which solely or at any rate mainly comprise ECG in small infants, particularly under the age of 2 years. Furthermore, that the materials from various authors are very different with regard to the percentage distribution of the various degrees of severity of the disease, presumably to be ascribed to the various criteria on which the patients are selected after the examination. In this review of ECG changes in VSD, the "normal" distribution of the various types of ECG changes in the material is not described, as such a "normal distribution" is not available, although for information it might be added that Keith (1966) gives the frequency of the various forms of ventricular hypertrophy in VSD in infants under the age of 2 years as: Normal: 16%, LVH: 18%, CVH: 52% and RVH: 14%. For children over the age of 2 years, the corresponding figures are: Normal: 32%, LVH: 34%, CVH: 21% and RVH: 13%.

Author's material

Introduction

In almost all the 144 patients in the material, 124 of whom were less than the age of 2 years at first cardiological examination, an electrocardiogram was made at least once during the first cardiological examination, with 3 standard limb leads, 3 unipolar limb leads (aVR, aVL and aVF) and 6 precordial leads: $V_1 - V_6$. Vector cardiography was not performed. All electrocardiograms were primarily evaluated by Ib Boesen, M.D., but also the author has evaluated all those electrocardiograms employed in the material, and in the few cases where there was disagreement between the two descriptions, that of the author has been employed.

Norms employed in the present material

The electric axis was determined on the lines of a diagram given by Nadas (1957) and checked according to a table given by Warburg (1946): normal axis: 0° - $+90^{\circ}$, left axis deviation: 0° - -90° , right axis deviation: $+90^{\circ}$ - $+180^{\circ}$, and excessive right axis deviation: $+180^{\circ}$ - -90° . The determination of ventricular hypertrophy (or lack of this) followed the values given by Keith et al. (1958). (These norms were also those employed in the daily work in the hospital.) For the determination of branch block, the norms given by Nadas were used (1957).

The electric axis

In the 119 of the 124 infants with isolated VSD who had a first cardiological examination before the age of 2 years, and in whom the ECG could be used for evaluation (of both electric axis and ventricular hypertrophy), the axis distribution was found to be as follows: no axis deviation: 47%, left axis deviation: 19%, right axis deviation: 34%.

Ventricular hypertrophy

The distribution of ventricular hypertrophy in the material of the 119 of the 124 infants who were examined before the age of 2 years was as follows: no ventricular hypertrophy 22%, left ventricular hypertrophy 4%, combined ventricular hypertrophy 62% and right ventricular hypertrophy 12% (cf. above). As a large proportion of the patients in the material were less than 4 months of age at this first cardiological examination - about 43% of the infants examined before the age of 2 years (see table 19, page 52) - this tendency to right ventricular hypertrophy found in the electrocardiogram in these first months of life is at any rate to a certain degree "congenital", and would have disappeared if the infant had been examined later and had not had any abnormality.

ECG-constellations

Grouping the ECG constellations: electric axis + ventricular hypertrophy, according to the size of the left-to-right shunt, the pressure in the RV or PA,

and the size of the relative volume of the heart, then the lowest values of these magnitudes are found in those cases where the ECG shows no axis deviation or ventricular hypertrophy. Apart from this, the distribution of the various ECG constellations with respect to shunt size is found to be more or less uniform, although there are clearly more examples of the ECG constellation LAD + CVH in infants with the large shunts. With regard to the distribution of the various ECG constellations within the various special ECG groups in RV or PA, then apart from the above, there is a tendency for those constellations in which CVH or RVH appear to be found particularly in infants with high pressure in RV or PA. In the case of the distribution of the various ECG constellations in the various groups of relative volume of heart, those constellations in which CVH or RVH are found have a tendency to accumulate among infants with slightly enlarged hearts.

P_{II} : Among the 124 infants examined before the age of 2 years, 34 cases were found in whom P_{II} was higher than 2.5 mm (which is reported as being the maximum normal). Of these, 5 had a systolic pressure in the RV or PA of 0-40 mm Hg, 11 a pressure of 41-60 mm Hg and 18 a pressure of $\geq$ 61 mm Hg (i. e. respectively 15%, 32% and 53% compared to the normal distribution in the material, according to the pressure values given, of 28%, 27% and 45%). There is thus a tendency for the P_{II} -increase to occur more frequently than expected in pulmonary hypertension (85% compared to an expected 72%). Assuming a normal systolic pressure in the RA of $\leq$ 6 mm Hg (Kjellberg et al. 1955), 7 of the 34 patients with higher P_{II} are found to have an elevated pressure in the RA (varying from 7 to 11 mm Hg). In these 7 cases, the systolic pressure in the RV varies correspondingly from 52 to 92 mm Hg.

Block

There was no case of complete branch block in the material, and only one case of incomplete right branch block (patient no. 755). Nor was any case of complete or incomplete a-v block in the material.

In the present material, the diagnostic value of the various isolated ECG findings for the diagnosis "isolated VSD" is limited.

ECG and hemodynamics

The importance of the ECG for the hemodynamic evaluation of the infants with

isolated VSD in the material, in the case of the electric axis alone, showed no correlation between the direction of this and pressure in the RV or PA.

It has been possible to show that slight cases of isolated VSD with normal or only slightly elevated pressure in RV or PA, and small left-to-right shunts, rarely result in abnormalities in the ECG with respect to the constellation: electric axis + ventricular hypertrophy; that high pressure in the RV or PA most often gives CVH or RVH (this is in contrast to the findings of Bender et al. 1958), and that patients with large left-to-right shunts often have LAD + CVH; finally, that the biventricular hypertrophy - reflected in CVH on the ECG - dominates the material in this low age group. These findings are in agreement with what most other authors have noted. The combination LAD + RVH was only found in a single patient in the material (patient no. 297).

Chapter VI

The diagnostic value of clinical examination + radiological examination of the thorax + ECG

Table 25 shows the number of children in whom isolated VSD was diagnosed as a result of a combination of clinical examination, radiological examination of the thorax and ECG (in children with VSD, including 124 under the age of 2 years at first cardiological examination), as well as the number of children in whom the type of heart disease was not diagnosed as a result of the combination of examinations mentioned, but only after further examinations. These results are grouped according to age at first examination and to the hemodynamic circumstances. As expected, it is seen that the diagnosis of VSD was difficult in the quite small infants, and that the diagnostic certainty increased with age. Furthermore, it appears that the diagnosis of VSD was made more easily at low pressures in the right half of the heart (where the localization of the systolic murmur was most often typical) than at high pressures, while the frequency with which the diagnosis of VSD was made as the result of clinical examination + radiological examination of the thorax + ECG, does not appear to depend on the size of the shunt. The diagnostic certainty of finding VSD on the basis of the clinical examination + the radiological examination of the thorax + ECG is thus not so great that further examination by means of cardiac catheterization and possibly angiocardiology becomes superfluous (as pointed out by Boesen 1955). See also chapter IX (page 82).

For the sake of completeness, table 26 also shows the number of patients - out of the total of 884 patients who underwent catheterization in the hospital during the period of examination discussed here - in whom an erroneous diagnosis of isolated VSD was made following clinical examination, radiological examination of the thorax and ECG, as well as the presumably correct subse-

Table 25. The 144 children in the material with verified isolated VSD (124 of them under the age of 2 years at first cardiological examination), grouped according to whether the diagnosis was made (80 children) or was not made (44 children) already at the first clinical (anamnestic and physical) examination + roentgenogram of thorax and ECG. The two groups are distributed according to age at first examination, pressure in RV in mm Hg, and size of left-to-right shunt (expressed by the oxygen deficit from RV to RA in %).

Age at first exam.	total	Diagnosis made at first cardiological exam. on clinical findings, roentgen. of thorax + ECG	Diagnosis not made alone on clinical exam., roentgen. of thorax and ECG
total	144	93	51
< 1 month	3	1	2
1 month	9	4	5
2-3 months	41	26	15
4-5 months	18	11	7
6-11 months	32	20	12
12-17 months	14	13	1
18-23 months	7	5	2
total < 2 yrs	124	80	44
≥ 2 yrs	20	13	7

Pressure in RV in mm Hg	total				
0-25	19	< 2 yrs	15	13	2
		> 2 yrs	4	3	1
26-40	30	< 2 yrs	20	17	3
		> 2 yrs	10	7	3
41-60	35	< 2 yrs	34	20	14
		> 2 yrs	1	1	0
≥ 61	60	< 2 yrs	55	30	25
		> 2 yrs	5	2	3

Oxygen deficit RV to RA in %					
0-9	40	< 2 yrs	31	18	13
		> 2 yrs	9	8	1
10-14	36	< 2 yrs	30	24	6
		> 2 yrs	6	2	4
15-19	35	< 2 yrs	32	18	14
		> 2 yrs	3	2	1
≥ 20	33	< 2 yrs	31	20	11
		> 2 yrs	2	1	1

Table 26. The final diagnosis in 46 patients in whom isolated VSD was the original erroneous diagnosis on the basis of clinical and roentgenological examination and ECG, but where the diagnosis was subsequently amended wholly or in part, after the patients had undergone cardiac catheterization and/or angiocardiography, and where the diagnosis in a number of them was further confirmed either by thoracotomy or at autopsy. These 46 patients (43 of them examined before the age of 2 years) are among the 884 patients who underwent cardiac catheterization and/or angiocardiography at the Queen Louise's Children's Hospital from August 1954 to the end of 1963.

No.	Sex G/B	Born	Age in months at 1st exam.	Final diagnosis	Autopsy: Thoracotomy
1	G	16/2-54	6	VSD+ASD sec. + PDA	A
19	G	23/4-54	6	SV+PS+PFO+tricuspid atresia	T + A
21	B	10/2-54	9	SV+complete transposition	A
22	B	2/5-54	6	valvular aortic stenosis+VSD	A
25	G	8/8-54	3	uncertain diagnosis	
36	G	2/3-54	10	suspected heart disease	
46	G	16/11-53	17	AVC	
48	B	27/2-54	14	complete transposition+VSD+ASD	
51	B	6/4-54	13	PDA	
54	G	1/3-55	3	ASD+VSD	A
62	B	25/12-54	8	ASD+one aberrant pulm. vein	
67	G	8/6-55	2	ASD+VSD	
81	B	5/10-55	1	truncus arteriosus	A
93	B	17/8-54	16	ASD	
94	G	3/10-55	3	PDA	T
96	G	6/8-55	5	VSD+PDA	
133	B	14/4-56	2	coarctation of the aorta, inop. type	
142	G	11/4-56	3	PDA	T
149	B	31/10-55	13	ASD	
183	G	17/7-48	101	no heart disease	
190	G	3/7-54	30	ASD	
197	G	28/4-56	10	Fallot's tetralogy	
202	G	26/2-57	1	ASD+VSD	
206	G	13/10-56	6	VSD+suspected aortic stenosis	
209	B	21/2-57	2	endocardial fibroelastosis+VSD	A
265	B	10/7-57	3	tricuspid atresia	
296	B	31/12-57	1	AVC	A
310	B	12/2-58	2	aorticopulmonary window	A
329	G	15/3-58	3	VSD+PDA+abnormal course of left pulm. art.	A
399	G	18/12-58	2	coarctation of the aorta, op. type	
451	B	5/6-59	2	VSD+ASD	
455	G	29/3-59	5	AVC	
487	G	10/10-59	2	diagnosis uncertain	
553	G	27/2-58	30	no heart disease	
581	B	15/2-60	8	diagnosis uncertain	
594	B	5/10-60	3	ASD	A
624	B	18/1-61	3	Fallot's tetralogy	
636	G	23/11-60	6	VSD+PS	
637	G	30/12-60	5	ASD	
640	B	18/1-61	4	VSD+PS	
769	G	4/8-62	<1	coarctation of the aorta, op. type+PDA	A
771	G	25/5-62	3	corrected transposition +PDA	T + A
795	G	27/3-62	7	PDA	T
798	G	7/5-62	6	Dextrocardia (rotation) +VSD+PFO	A
844	G	20/1-63	4	complete transposition	
882	B	8/10-63	1	SV	

Abbreviations:

ASD = atrial septal defect, ASD sec. = atrial septal defect of secundum type, PDA = persistent ductus arteriosus, SV = single ventricle, PS = pulmonary stenosis, AVC = atrioventriculare commune, PFO = persistent foramen ovale

quent diagnosis, as a result of supplementary examinations (cardiac catheterization, angiocardiography, possibly operation or autopsy).

Chapter VII

Cardiac catheterization and selective right-sided angiocardiology

Introduction

After Forssmann in 1929, as the first man to do so, had introduced a catheter into one of his veins (quoted from Keith et al. 1958), 12 years were to elapse before Cournand and Ranges (1941) reported the first clinical application of catheterization of the right half of the heart.

The technique and the results obtained in catheterization of the right half of the heart and selective right-sided angiocardiology (the injection of contrast into a definite localization in the right half of the heart via the catheter which has been introduced) have since been reported by numerous authors (for literature and references see Kjellberg et al. 1955, F.H. Adams and Lind 1956, Boesen et al. 1956, Nadas 1957, Keith et al. 1958, Gøtzsche et al 1961, Merrild 1962).

Author's material

Technique employed in the cardiac catheterizations

In the present study, the technique of cardiac catheterization employed is that described by Boesen et al. (1956) and later by Merrild (1962). Reference should therefore be made to these studies for descriptions of the main features of the procedure, but as minor changes in the technique were introduced during the years from which the present material originates (1954-1963), certain details will be discussed.

The catheters used for the catheterization were of type "Lehman", with or

without end hole. At the start of the period, catheters were used with end hole, making it possible to measure the pulmonary capillary venous pressure, but as the risk of subendocardial or intrapericardial injection of contrast during the angiocardiology is greater when catheters are used with an end hole than without an end hole (the latter with only side holes at the tip), and as there was still great interest in performing angiocardiology, the practice increased more and more of using catheters with only side holes. The size of catheter has varied between no. 4 and no. 7, depending on the size of the vessel through which the catheterization is performed.

In the great majority of cases, it was possible to perform the catheterization through the long saphenous vein just below the inguinal ligament, but in 15 cases, however, this vein was so small that either the femoral vein or the cubital vein had to be used.

It should be noted that it was not possible to determine the oxygen uptake through the lungs. Furthermore, only in a very few cases was it technically possible to obtain determinations of the oxygen saturation from the arterial blood, thus limiting the possibility of calculating the size of the left-to-right shunt and calculating the resulting pulmonary vascular resistance, see page

. There was direct catheterization of the left ventricle through the septal defect in 11 cases (patients no. 170, 262, 273, 277, 297, 323, 334, 542, 547, 678 and 700). In one case, the left ventricle was catheterized through the left atrium. In one case, the aorta was presumably catheterized through a quite thin ductus arteriosus (2 mm thick, verified at operation), without shunt.

A total of 149 catheterizations were performed at the first examination of the 144 children, 127 of these catheterizations being performed in the 124 infants who were under 2 years of age at the first investigation. In 5 cases, 2 catheterizations were performed at the first examination, as the first catheterization had not given the necessary information. In 2 cases, a venous angiocardiology was first performed on account of the poor condition of the infant, but this had to be supplemented by means of a cardiac catheterization + selective angiocardiology, because the diagnosis could not be established on the first investigation. In 2 cases, after the first cardiac catheterization + angiocardiology, it was necessary to supplement this investigation with a venous angiocardiology, for the same reason. All these last 4 patients were under 2 years of age at this first cardiological examination.

On account of the often very poor general condition and cardiac state of the children, an effort was made to carry out the catheterization as rapidly as possible, not to attempt to force the catheter out into the pulmonary artery if this proved difficult or involved electrocardiographic disturbances, and finally to take as few blood samples as possible so as to reduce the blood loss to the minimum.

Complications in the cardiac catheterizations

In no case did the complications listed below result in permanent sequelae for the child, and only in a few cases did the complications persist longer than the actual period of catheterization. There were no deaths from catheterization in the material, but for the sake of completeness it should be mentioned, that in the material in the cardiological laboratory, one patient with VSD died during the investigation. However, this patient has not been included in the present material, as no useful catheterization results were obtained in this case.

Respiratory failure of brief duration during the investigation: 4 cases (no. 23, 335, 571 and 855).

Convulsions on recovery after the investigation: 1 case (no. 214).

Disturbances in cardiac rhythm (only during the investigation):

Premature beats: 2 cases (no. 37 and 103).

Supraventricular tachycardia: 3 cases (no. 2, 379 and 463).

Ventricular tachycardia: 1 case (no. 238).

Total a-v-block: 3 cases (no. 277, 415 and 416).

Atrial flutter: 1 case (no. 381).

Complications of hemostasis: 1 case (no. 191).

Purulent secretion from the "cut-down": 1 case (no. 299).

When the femoral vein was used as a vessel for the catheterization, cyanosis and edema of the limb in question were observed in 5 cases (no. 58, 88, 467, 547 and 550) for 1 to several days after the investigation, but in all these patients the leg recovered its normal appearance later. In 3 cases, where the femoral vein was used (nos. 49, 277 and 479), there was not even any acute effect on the venous drainage from the limb in question (see also under complications of angiocardiography).

Normal values for pressure and oxygen saturation used in the present material

In the case of the pressures, the normal values quoted by Rossi (1954) and Nadas (1957) and Keith et al. (1958) have been compared to the following normal values: systolic pressure in RA $\bar{<}$ 6 mm Hg. Systolic pressure/diastolic pressure in RV $\bar{<}$ 25/4 mm Hg and systolic pressure/diastolic pressure in PA $\bar{<}$ 25/10 mm Hg. A systolic pressure in RV between 26 and 40 mm Hg is regarded as belonging to a transitional group between the group with normal pressure and the groups with pulmonary hypertension, defined in the present study as cases with a systolic pressure in RV or PA $\bar{>}$ 41 mm Hg. For comparison, Edwards

(1957) states that a value of 25 mm Hg is a normal pulmonary artery-systolic pressure, but that the boundary between normal and elevated pressure is not sharp.

In normal subjects, there may be a difference in the systolic pressure in RV and PA, so that the PA pressure is slightly lower than the RV pressure (without a pulmonary stenosis being present), but this difference does not exceed 8 mm Hg (Kjellberg et al. 1955). (After the age of 2 weeks, the pressure in RV, PA and LA in normal infants are the same as in adults (Keith et al. 1958)). In the case of patients with VSD, Kjellberg et al. (1955) and Farrar and Dunlop (1965) put the limit for the size of the pressure gradient between RV and PA at 20 mm Hg for the systolic pressure, while Fyler et al. (1958) reckons with a normal pressure gradient < 25 mm Hg. If, however, 8 mm Hg is chosen to be the maximum permissible pressure gradient between RV and PA, then the conditions in the present material become as follows:

In the present material of 144 children, 124 of them under 2 years of age, the decisive catheterization at the time of the first cardiological examination did not include catheterization of the PA in 22 cases, but only the RV (of these 22, only one was over the age of 2 years), and in one, only the PA was catheterized, not the RV. In 103 patients, the systolic pressure change from RV to PA was from +4 mm Hg to -8 mm Hg, which according to the limits discussed is accepted as being equal to "no change in pressure". In 5 patients (no. 207, 238, 291, 719 and 858, all over the age of 2 years), the systolic pressure in PA is from 6 to 14 mm Hg higher than in RV. There is no satisfactory explanation for this difference. It may be due to the pressure in the RV having been measured slightly too low, because one of the catheter holes may have been lying in the RA, so that the resulting "RV-pressure" has become lowered. Kjellberg et al. (1955), however, state that an elevated pressure in LA, on account of failing LV, can explain an elevated pressure in PA. However, as the PCV-pressure was not measured in the 5 patients quoted, it is not possible to evaluate this explanation in the present material. In 12 of the patients (all over 2 years of age) the systolic pressure in the RV was from 9 to 18 mm Hg higher than the systolic pressure in the PA. All the patients, with the exception of one (patients nos. 5, 58, 88, 111, 297, 323, 338, 556, 700, 721, 759 and 789) had pulmonary hypertension; the last patient, no. 721, had a systolic pressure of 39 mm Hg in the RV; the systolic pressure was an average of 61 mm Hg, varying from 45 to 82 mm Hg. Of these 12 patients, only one (no. 721) had a small left-to-right shunt, with an oxygen saturation deficit from RV to RA of 6%, 6 of the patients (nos. 297, 323, 556, 700, 759 and 789) had a moderately large left-to-right shunt, with an oxygen saturation deficit of 13-19%, and 5 of the patients (nos. 5, 58, 88, 119 and 338) had large left-to-right shunts

with oxygen saturation deficits of 28-59%. The explanation for this fall in pressure from RV to PA may be that there has been a relative pulmonary stenosis, which supposition is supported by the fact that a moderately large to very large left-to-right shunt was found in all patients with the exception of one (no. 721), as stated. The results obtained by Garcia et al. (1960), Sandøe (1963) and Watson and Lowe (1965) should be compared with this, as they found the pressure gradient secondary to the large arteriovenous shunts. In spite of the pressure gradient mentioned, all the above patients were diagnosed as having isolated VSD, on the grounds of the results obtained in the remainder of the investigations, especially the angiocardiograms.

With regard to the determinations of oxygen saturation, the cardiological laboratory where the present study was carried out laid down the condition that for an oxygen saturation deficit to be significant, the difference between the average oxygen saturation in the venae cavae and the oxygen saturation in the RA should be $\bar{\geq}$ 10%, between RA and RV $\bar{\geq}$ 7.5%, and between RV and PA $\bar{\geq}$ 5%. The reason for these requirements being slightly stronger than those reported by others is due above all to the number of samples from each localization being so small, because of the low age of the infants and their poor condition.

Provided it has been technically possible, at least one blood sample for oxygen saturation determination has been obtained from each site of significance for the diagnosis, on each catheterization, i. e. venae cavae, RA, RV, PA and possibly LA, LV and aorta. Where it has been considered justifiable, more than one sample has been taken from each site.

Review of the cardiac catheterizations

The diagnosis of VSD has been made on the basis of the oxygen saturation determinations, when the difference between the oxygen saturation of RA and RV (possibly PA) has been $\bar{\geq}$ 7.5%, provided a shunt from LA to RA could be excluded, and provided catheterization showed it to be unlikely that there was a persistent ductus arteriosus or an aortico-pulmonary window.

In the total material, there has been at the first (decisive) catheterization an average of 1.5 oxygen analyses in the VCI, 1.2 in the VCS, 2.9 in the RA, 2.5 in the RV and 2.0 in the PA (the corresponding figures only for the 124 infants under 2 years of age are: 1.3 oxygen analyses in the VCI, 0.8 in the VCS, 2.3 in the RA, 2.2 in the RV and 1.7 in the PA). With regard to the pressure measurements, in the total material there were on the average 1.0 pressure measurements in the RA, 1.1 in the RV and 1.1 in the PA (correspondingly, alone for the 124 infants under 2 years of age: 1.0 pressure measurements in

the RA, 1.1 in the RV and 1.1 in the PA). In addition, oxygen analysis samples were obtained in 1 patient from the left superior caval vein, in 1 patient from the vena hemiazygos, in 2 patients from the subclavian vein, in 1 patient from a pulmonary vein, in 25 patients from the LA, in 7 from the LV, in 1 from the carotid artery, in 1 from the coronary sinus and in 5 from the aorta.

The values used for the oxygen saturation have been average oxygen saturation in caval veins, average oxygen saturation in RA, average oxygen saturation in LA, and average oxygen saturation in PA, LV and aorta. In the great majority of the total of 144 patients, the oxygen saturation value in RV is given as the mean value of the individual values found for the oxygen saturation (a total of 118 patients). In this group of patients, only one sample has been taken in the RV in many cases, but where there have been several samples from the RV, it has not been stated in this group of patients where the samples were taken in the RV (due to the very small space conditions in the very small infant, which made it impossible by fluoroscopy to evaluate precisely the position of the catheter tip at the moment of taking the sample). This group of patients also includes those patients in whom a measurement of the oxygen saturation in PA was not made, either because it was technically impossible to catheterize the PA or because the infant had been too ill, or arrhythmia had been triggered-off during the attempt to introduce the catheter into the PA.

However, where it is reported that one or more of the oxygen saturation determinations were made in the outflow tract of the RV, this value or the mean value of these has been used. This was the case in a total of 11 patients (nos. 5, 16, 88, 401, 522, 550, 556, 607, 700, 716 and 755).

In those cases where the oxygen saturation in PA (or its mean value) has been equal to or more than 5% above the mean of the oxygen saturation in the RV or the outflow tract of this, this mean value of the oxygen saturation percentage in the PA has been used in calculating the left-to-right shunt. The reason was that these cases must have involved patients in whom the blood streaming through the VSD runs directly into the PA without mixing to any significant extent with the blood in the RV, provided that a persistent ductus arteriosus or an aortico-pulmonary window could be excluded or demonstrated to be unlikely, as a result of the other investigations carried out. This has been the case in a total of 15 patients (nos. 23, 47, 58, 236, 238, 247, 268, 273, 276, 338, 407, 571, 726, 764 and 864). In the last two groups of cases, the VSD must be assumed to have had a position high up in the interventricular septum, just below the pulmonary ostium (cf Reynolds 1966: the supracristal VSD), while the usual case is for the defect to lie below the crista supraventricularis, so that here the blood through the defect must pass around the crista, whereby it becomes mixed with the other blood in the RV (Joly et al. 1951, Kjellberg et al.

1955). The value of 92% has been used as the lower limit for normal oxygen saturation in LA and LV (the value chosen by Nadas 1957, Sandøe 1963 and Farrar and Dunlop 1965). Other investigators have used a greater lower limit: Kohout et al. (1955): 93%, Agustsson et al. (1957): 94%.

The pressure in RA, RV and PA (possibly also in LA and LV), has been noted directly as measured. The figure given for the pressure in RV or PA is the systolic pressure. On the other hand, as already mentioned, it has not been possible to make a determination of the flow through the defect or to determine the pulmonary vascular resistance, because the oxygen uptake via the lungs could not be examined in the material, and the arterial oxygen saturation could only be determined in very few of the patients. The difference in oxygen saturation in per cent between RV and RA has therefore been employed as an expression for the shunt size, and an expression for the vascular resistance has been obtained in patients with pulmonary hypertension by assuming that the magnitude of the shunt (determined as indicated), varied inversely with the size of the pulmonary vascular resistance. Table 27 shows the significance of the size of the pressure in the RA. It is seen that 18 patients (= 15%), all under 2 years of age at the first cardiological examination, had a systolic pressure in the RA > 6 mm Hg. The incidence of elevated pressure in the RA in VSD is reported very variably, from 4% (Kjellberg et al. 1955) more than 7% (Garcia et al. 1960) and 8% (Sandøe 1963), to 17% (Blount et al. 1955). The incidence in the present material thus approaches most closely the report of the last authors. In addition, this increase in pressure is seen to be present only in pulmonary hypertension, and here in particular in cases with pressure equalization between the ventricles, whereas the increase in pressure in RA does not appear to be correlated with the size of the shunt, as was found to be the case by Sandøe (1963) in a mainly adult material. Garcia et al. (1960) found no correlation with pressure in the RV.

Selective right-sided angiocardiology

In the present material, selective angiocardiology - in all cases right-sided - was carried out in almost all patients during the first few years after the cardiological laboratory was started at Queen Louise's Children's Hospital in 1954 (for the technique, see Lind et al. 1960). In the course of time, however, the tendency has gradually been to go over increasingly to performing selective angiocardiology for certain congenital heart diseases including VSD, only if the diagnosis was not certain on the basis of cardiac catheterization alone, i. e. from oxygen saturation determination and possibly catheterization of the VSD

Table. 27. Magnitude of the pressure in RA in relation to the magnitude of the pressure in RV, and to the size of the left-to-right shunt (expressed by the oxygen deficit from RV to RA in %), in 143 children with isolated VSD, 123 of them under 2 years of age at first cardiological examination. (The pressure measurement in RA was not available in one patient).

Table 27

Pressure in RV in mm Hg	Pressure in RA $\leq$ 6 mm Hg						total pressure $\leq$ 6 mm Hg	Pressure in RA $>$ 6 mm Hg						total pressure $>$ 6 mm Hg	total number pts.
	< 2 yrs			≥ 2 yrs				< 2 yrs			≥ 2 yrs				
	not operated on alive	operated on alive	dead	not operated on alive	operated on alive	dead		not operated on alive	operated on alive	dead	not operated on alive	operated on alive	dead		
0-25	14	0	0	0	4	0	0	0	0	0	0	0	0	0	18
26-40	19	0	0	1	10	0	0	0	0	0	0	0	0	0	30
41-60	25	0	3	2	1	0	0	0	0	2	1	1	0	0	35
≥ 61	18	3	11	9	4	0	0	1	4	1	3	6	0	0	60
total	76	3	14	12	19	0	0	1	4	3	4	7	0	0	143

Size of left-to-right shunt																	
0-9%	21	1	1	3	9	0	0	0	1	2	0	1	0	0	0	4	39
10-14%	21	0	3	4	6	0	0	0	0	0	0	2	0	0	0	2	36
15-19%	18	1	6	2	3	0	0	0	0	2	0	2	1	0	0	5	35
$\geq 20\%$	16	1	4	3	1	0	0	1	1	1	2	3	0	0	0	7	33
total	76	3	14	12	19	0	0	1	4	3	4	7	0	0	0	18	143

itself. The aim was not to prolong the investigation and to reduce the exposure of the patient to radiation, as well as to avoid the (few) complications which can be ascribed to angiocardiology.

In the daily routine, all the angiocardigrams were described by the permanent radiological consultant of the hospital, Physician-in-Chief, dr. med. Th. Rosendal. All the films (picture series), but not those few cases where a film was made of the screen picture alone during the injection of contrast, have later been reviewed by the author, and it is the author's description of the pictures which has been used in the study. This description has been compared with the radiologist's description, and there have only been minimal divergencies. In the few cases where no more than the fluorescent screen picture has been filmed, the description of this recording (by Professor J. Lind) has been used alone.

Complications in the angiocardiology itself

In the present material, complications resulting from the selective angiocardiology (i. e. complications not determined by the actual catheterization) occurred in a total of 5 patients (in one, no. 68, in 2 examinations, and in one, no. 49, there have been 2 complications). The complications and the patients in whom they have occurred have been:

Tachycardia on injection (no. 49).

Subendocardial injection of contrast (nos. 68, 103, 224 and 518).

Furthermore, a type of complication observed has been catheter recoil during the injection in 2 patients (nos. 98 and 244).

A total of 89 selective angiocardigrams have been made and 5 venous angiocardigrams (4 purely venous and 1 in which heart catheterization was commenced, but for technical reasons angiocardiology had to be carried out via the long saphenous vein and not through the catheter (no. 787)). In 3 patients, 2 angiocardigrams were made following the first cardiological examination (nos. 2, 29 and 269), and in 4 cases, a new angiocardigram was made at a later time than the first investigation (nos. 29, 47, 58 and 68).

Strikingly wide central and narrow peripheral pulmonary vessels were seen (see page 54) in the angiocardigrams in only 2 patients (nos. 37 and 247 - with a systolic pressure in the RV of 49 and 70 mm Hg, respectively, and an oxygen saturation difference in RV to RA of 32% and 14%, respectively), but these findings have not been convincing, and were not observed among the 5

patients who were found on follow-up examination to have developed Eisenmenger's syndrome (page 124).

In the first cardiological examination, the diagnosis of VSD was made by direct visualization of the defect using angiocardiography in 11 cases (all selective), by signs of recirculation of contrast in the pulmonary circulation in 75 of the selective angiocardiograms and in 3 of the venous angiocardiograms, by dilution of contrast on transition from RA to RV in 9 of the selective angiocardiograms and 2 of the venous angiocardiograms, by simultaneous filling of both ventricles in 8 cases, all selective angiocardiograms, and by a strong contrast filling of the PA together with a weak filling of the aorta in 25 of the selective angiocardiograms (here, however, by injection into the left side of the heart). Thus, there are a number of patients in whom several of the findings mentioned have been present in the same patient.

Direct visualization of VSD

An examination was made of those 11 patients in whom VSD was visualized directly by angiocardiography, to determine whether this visualization took place in those particular cases because the pressure in the RV has been high, possibly equal to the pressure in the LV (which was to be expected). In 10 of the 11 patients (nos. 17, 23, 37, 98, 119, 207, 236, 276, 381 and 807), pulmonary hypertension was present (i. e. systolic pressure in the RV $\geq$ 41 mm Hg), and in 6 of these 10 (nos. 23, 98, 207, 236, 276 and 381) the systolic pressure in the RV has been from 66 to 82 mm Hg, i. e. presumably the same pressure in the RV as in the LV. Only in 1 patient (no. 178) was the systolic pressure in the RV normal (= 27 mm Hg).

Final remarks

To conclude, it may be said that cardiac catheterization and possibly angiocardiography (in almost all cases selective), have been decisive for the diagnosis of VSD, and for determining the hemodynamic conditions (see next chapter), and hereby for evaluating the degree of severity of the individual case, although the clinical investigations previously mentioned have given some indication as to the nature of the disease and its degree of severity. These cardiac catheterizations + angiocardiographies were carried out in often very ill and very small infants, without any deaths (see however the reservation on page 66), and with

rather few and transient complications. Such investigations will continue to be justified, whenever problems arise as to diagnosis, indications for and possibilities of treatment, in a patient in whom the presence of isolated VSD is suspected.

Chapter VIII

Hemodynamics

Review of the literature

The hemodynamic conditions in the first two years of life in patients with isolated VSD

In patients with isolated VSD which has been "established" as early as the 4th-7th week of intrauterine life (Keith et al. 1958) and where the fetal circulation is as in normal subjects (Dammann et al. 1960, Edwards 1960), apart from this extra connection between the right and the left ventricles, functioning more or less like a ductus arteriosus, there will after birth be a difference in the hemodynamic (and clinical) picture depending on: a) the size and localization of the defect, and b) the magnitude of the pulmonary vascular resistance.

The situation is that if the septal defect is below a certain critical size ($1 \text{ cm}^2/\text{m}^2$ surface of the patient), it is still able to keep up a pressure gradient between the ventricles. The value of this systolic pressure gradient is inversely proportional to the size of the defect (in contrast to the state of affairs in the case of large ventricular septal defects). With such small septal defects, the pulmonary vascular resistance does not play so great a role for the distribution of the blood between the two circulations, but may nevertheless result in a certain rise in pressure in the pulmonary circulation. If the ventricular septal defect exceeds the critical size mentioned, the right and left ventricles function as one ventricle, and have a "common ejectile force". In this situation, there is pulmonary hypertension of the order of magnitude of the pressure in the greater circulation. In such cases, it is the degree of severity of the pulmonary vascular resistance, by comparison with the vascular resistance of the greater circulation, which will determine the value of the shunt from

left to right (or possibly from right to left). The right pulmonary vascular resistance contributes to the maintenance of a more or less large systemic flow (H. J. C. Swan et al. 1958, Burchell 1959, Savard et al. 1960, Lynfield et al. 1961). Certain authors do not employ the area of the defect in relation to the surface of the patient in m^2 , but quote the diameter of the defect, where the limiting value is 1 cm/ m^2 surface (E. H. Wood 1958, Dammann et al. 1960, Lucas et al. 1961), or the size of the defect is quoted in relation to the size of the aortic ostium (for literature and references see Becu et al. 1956).

Pulmonary hypertension in isolated VSD

The concept of pulmonary hypertension refers to an increased pressure in the pulmonary artery (and in the RV). A value of 25 mm or below for the systolic pressure is reckoned to be normal, but there is no sharp boundary between normal and elevated pressure. Significantly elevated values of systolic pressure in the PA are reckoned as 40 mm Hg or above (Nadas et al. 1959). Values below 40 mm Hg are described as "slight" by Swan et al. (1954) and as hemodynamically benign by Lynfield et al. (1959 b). Whitaker (1958) calls values below 50 mm Hg "only slightly elevated". The pulmonary hypertension in VSD is due to a combination of 2 factors: the one is a large left-to-right shunt through the VSD to RV and further into the pulmonary vascular circulation (a hyperkinetic hypertension), while the other is a pulmonary vascular resistance in the pulmonary vascular tree, due to the vascular reaction to the large flow and the high pressure which causes this flow in the pulmonary vessels (an obstructive hypertension). In very young infants, the pulmonary hypertension is to a very great degree hyperkinetic, but gradually, although to a lesser degree, it will be the result of the natural increase in the pressure in the left ventricle, and - more important - the result of the pulmonary arteriolar resistance, which increases with age; in other words it will become mainly obstructive hypertension (Brotmacher and Campbell 1958). In infancy, a rather large left-to-right shunt is maintained through the VSD, in spite of the pulmonary vascular resistance which persists in many cases from fetal life (Keith et al. 1958), but everything else being equal, the flow is greater, the smaller the pulmonary resistance.

The shunt through the defect in the isolated VSD

The blood flow - the shunt - is determined in cases of small VSD (i. e. those

with an area less than $1 \text{ cm}^2/\text{m}^2$ surface of the infant) by the size of the septal defect. The greater the area of the defect, the greater the blood flow through the defect. In cases of large VSD (greater than the size limit mentioned) the magnitude of the blood flow through the defect is determined not only by the size of this, but also by the relationship between the resistance in the greater circulation and in the smaller circulation. The smaller the resistance in the smaller circulation, the greater the flow through the defect.

The pulmonary vascular resistance in isolated VSD

The increased pulmonary vascular resistance is the result on the one hand of the abnormal pressure and flow conditions in VSD, and presumably also of the muscular tone in the pulmonary arterioles and of the pressure in the left atrium and pulmonary veins, while on the other hand, the increased pulmonary vascular resistance, together with the size of the VSD, determine the magnitude of the pressure in the RV or PA and the size and direction of the shunt, and thereby in the last instance the prognosis in the individual patient.

Under the age of 2 years, it is exceedingly rare for such a high pulmonary vascular resistance to be present that either a mixed left-to-right and right-to-left shunt develops or a properly developed Eisenmenger's syndrome with purely right-to-left shunt. Reduced oxygen saturation in the arterial blood, i. e. a degree of oxygen saturation in the LV $< 92\%$ (see page 70) will point to the presence of an intermittent and permanent right-to-left shunt, as many investigators have been unable to demonstrate inadequate oxygenation of the blood in the lungs (Bing et al. 1947, Selzer 1949, Selzer and Laqueur 1951, Goldberg et al. 1951, Voci et al. 1952). However, it is not possible to exclude the presence of precapillary arteriovenous anastomoses in the lungs and inhibited oxygen diffusion in the lungs in the case of very large left-to-right shunts, as the cause of reduced oxygen saturation in the pulmonary veins, as pointed out by Kjellberg et al. (1955), but if the left-to-right shunt is small or possibly equal to zero, and if the arterial oxygen deficit is high without it being possible to demonstrate precapillary anastomoses in the lungs, the probability that a right-to-left shunt is present is very great.

Finally, it should be mentioned that some authors have considered that there may exist a "pulmonary vascular obstruction syndrome" which may be present together with congenital heart diseases, although not necessarily with a causal relationship to them. The genesis is uncertain (Cutler et al. 1954, Neill and Taussig 1959).

Hemodynamic grouping

Series consisting of patients with isolated VSD have been grouped in various ways by a number of authors, particularly with respect to an evaluation of the spontaneous prognosis, and for the selection of the subjects most suitable for operative treatment. (For indications for operation, see chapter XI on operations, page 87).

A number of authors (Kjellberg et al. 1955, Mannheimer et al. 1957, Brotmacher and Campbell 1958, Keith et al. 1958, Veasy 1960, Lynfield et al. 1961, Kidd et al. 1965a, Ritter et al. 1965, Storstein and Sörland 1966) have used a purely hemodynamic basis for the grouping, which in a slightly modified form is as follows (only those authors have been considered whose series contain patients under 2 years of age):

- I Small VSD where the shunt cannot be demonstrated or is a small left-to-right shunt, normal or almost normal pressure in RV or PA.
- II a Pronounced left-to-right shunt, normal pressure in RV or PA.
- II b Pronounced, possibly large left-to-right shunt, slightly increased pulmonary vascular resistance and moderately increased pressure in RV or PA.
- III Increased vascular pulmonary resistance and pronounced increase in the pressure in RV or PA, with a slightly smaller pressure or the same pressure as in the greater circulation, but with left-to-right shunt maintained.
- IV Strong pulmonary vascular resistance and pulmonary hypertension, with a pressure in the RV or PA $\bar{>}$ LV, as well as a small mainly right-to-left shunt (with a tendency to cyanosis).

Other authors have used a combined hemodynamic and clinical grouping, which with small modifications can be described as follows (only those authors have been considered whose series contain patients under 2 years of age: Kay et al. 1957, Neill and Taussig 1959, Blount and Woodwark 1960, Kaplan et al. 1963, Ash 1964):

- I Slight defect with small left-to-right shunt, normal pressure in right ventricle. Normal pulmonary resistance. No enlargement of the heart.
- II Moderately large defect with moderate left-to-right shunt and enlargement of the heart. Little or no increase in pressure in RV. Little or no increase in pulmonary vascular resistance.
- III Large defect with pronounced enlargement of the heart, large left-to-right shunt or severe pulmonary hypertension. Increase in pulmonary vascular resistance; with or without cardiac failure in infancy.

- IV Large defect with considerably increased pulmonary vascular resistance. Varying size of heart. Pressure in RV $\bar{>}$ pressure in LV. Increasing cyanosis.

Finally, as a basis for classification, one single group of investigators (Lucas et al. 1961) have grouped their material according to the development of the pulmonary vascular resistance:

- I Normal fall in total, pulmonary vascular resistance with age.
A: small VSD ($< 1 \text{ cm}^2/\text{m}^2$ surface).
B: apparent fall in relative VSD size.
C: large VSD.
- II Delayed fall in total, pulmonary vascular resistance.
Large VSD.
- III No fall in the total, pulmonary vascular resistance.
Large VSD.
- IV Increasing total, pulmonary vascular resistance after a normal decrease from the stage of fetal life. Large VSD.
- V Cyanotic patients. The development to a high pulmonary vascular resistance is not known. Large VSD.

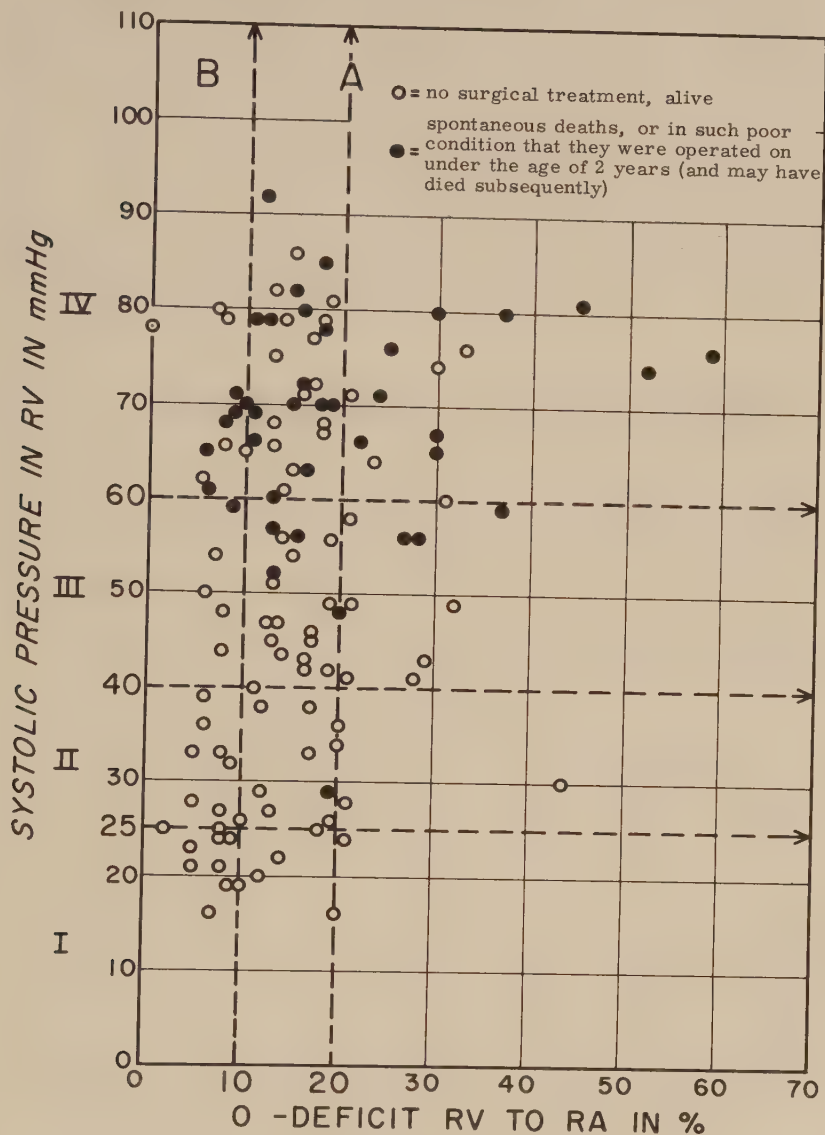
The first two methods of classification mentioned do not differ essentially from each other.

Author's material

As mentioned in the previous chapter, it has not been possible to carry out those measurements necessary to determine on the one hand the size of the shunt flow and on the other hand the pulmonary vascular resistance. An impression has been obtained of the size of the shunt by using the difference in the oxygen saturation between RA and RV or PA, and in the case of the pulmonary vascular resistance, it was considered that in patients with almost or complete pressure equalization between RV or PA and LV, the size of the shunt could be used as an indicator for the magnitude of the pulmonary vascular resistance, this being considered to be greater the smaller the shunt, and conversely.

Fig. 11 shows the relationship between the magnitude of the pressure in RV or PA in mm Hg, and the size of the left-to-right shunt, expressed as the oxygen saturation deficit RV to RA in per cent, in the 124 children of the material who were all under the age of 2 years at the time of the first cardiological examination. Furthermore, those patients are indicated who had the

Fig. 11. Relationship between the value of the systolic pressure in the RV in mm Hg and the size of the left-to-right shunt, expressed as oxygen deficit RV to RA in %, in 124 children with isolated VSD, under the age of 2 years at first cardiological examination.



poorest clinical condition, either dying spontaneously, or being in such a poor condition that they were referred for palliative or, in a few cases, corrective operation, following which a number of them died. The figure shows that all the patients who were in a poor clinical condition had a pressure in RV or PA ≥ 48 mm Hg, and by far the majority even above 60 mm Hg, which is presumed to correspond to the pressure equalization between the right and left ventricle. With regard to the size of the shunt, the patients who were in a poor condition are distributed more or less uniformly among the higher pressure groups. In the groups with a pressure in the RV or PA ≤ 40 mm Hg, i. e. normal or only slightly elevated pressure in the RV or PA, the shunt sizes are clearly smaller (with the exception of 1 case: patient no. 102).

Grouping of the material according to the hemodynamic conditions

It was considered possible to group the material of 124 children who were examined for the first time before the age of 2 years, along the lines of the groupings by the authors mentioned in the review of the literature, who used a purely hemodynamic basis, as follows:

- I normal pressure in RV or PA, varyingly large (not more than 21% oxygen deficit from RV to RA) left-to-right shunt (small defects): a total of 15 patients, none dead or operated on.
- II only slightly elevated pressure in RV or PA, varyingly large (not more than 21% oxygen deficit in RV to RA, with the exception of 1 patient no. 102) left-to-right shunt (large defects): a total of 20 patients, 1 undergoing corrective operation but dying in the course of this.
- III considerable increase in pressure in RV or PA, but with the pressure gradient maintained between RV or PA and LV, with varyingly large left-to-right shunt, in a number of cases large (up to 37% oxygen deficit RV to RA). In the cases with the rather small shunts, presumably rather high pulmonary vascular resistance, while in the cases with the large shunts, presumably rather slight increase in the pulmonary vascular resistance: a total of 34 patients, 9 of them in such poor condition that there were either spontaneous deaths (2) or the patients were referred for palliative operation immediately after the examination (7, 3 of whom died after the operation).
- IV A strongly increased pressure in RV or PA with pressure equalization between RV or PA and LV, with moderately large or large left-to-right shunts (up to 59% oxygen deficit in RV to RA), and presumably only moderately in-

creased pulmonary vascular resistance: a total of 45 patients, 23 of whom were in such a poor condition that there were either spontaneous deaths (2) or they were referred for palliative (21) or corrective (3) operation immediately after the examination (8 of those undergoing palliative operation and all 3 undergoing corrective operation died after the operation).

IV B strongly increased pressure in RV or PA with pressure equalization between RV or PA and LV, with a small left-to-right shunt (i.e. < 10% oxygen deficit in RV to RA) and presumably strongly increased pulmonary vascular resistance: a total of 10 patients, 6 in such a poor condition that they either died spontaneously (2) or were referred for palliative operation immediately after the examination (4), 3 of the latter dying after the operation.

A corresponding grouping was made of the 20 patients in the material who underwent cardiological examination for the first time after the age of 2 years. 15 of these patients had a pressure in RV or PA $\bar{<}$ 48 mm Hg, and a small or moderate left-to-right shunt, none had a small left-to-right shunt corresponding to a large pulmonary vascular resistance, and only one was in such poor condition (no. 273) that a corrective operation was performed immediately after the examination, but without success.

The reason for separating group IV B particularly from the other patients (IV A) with the same pressure, is that group IV B presumably included those patients in whom in addition to a left-to-right shunt there might be a right-to-left shunt of a certain size, on account of the presumably large pulmonary vascular resistance.

Whether there are patients in group IV B with both right-to-left and left-to-right shunt, cannot be decided with certainty. Two of the 10 (no. 467, oxygen saturation deficit RV to RA: 6%, and no. 864, oxygen saturation deficit RV to RA: 0%) were cyanotic at the physical examination, and may presumably have had a right-to-left shunt in addition to a left-to-right shunt, at any rate in the case of no. 467. Cardiac decompensation as the cause of cyanosis, however, cannot be excluded in patient no. 864, but as this patient had no demonstrable left-to-right shunt, it would be reasonable to assume that a right-to-left shunt may have been present. Patient no. 467 had an oxygen saturation in LA of 95%, but the oxygen saturation in LV or in the peripheral arteries was not measured. In the other 8 patients, no definite oxygen saturation measurements are available. It is doubtful in some cases whether the lower boundary for the systolic pressure in RV or PA should lie actually at 61 mm Hg in order to reckon with a pressure equalization between RV or PA and LV. In the few (20) patients in

whom the investigation was carried out after the age of 2 years, it is at any rate certain that the limit should be increased with increasing age, as the systemic pressure increases with increasing age.

In the 124 patients examined before the age of 2 years, experience has set the boundary at the figure mentioned of 61 mm Hg in the RV or PA, but in the present material it has been found that the cardiac state in a patient may be so poor that the systemic pressure does not lie as high as around 61 mm Hg, and in such cases pressure equalization will be possible at a low pressure in RV or PA. This was found in patient no. 547, where the pressure in LV was also measured (pressure in RV: 48 mm Hg, in LV about the same, 46 mm Hg). These values were also found, although to a less pronounced degree, in patients no. 47 and 542 (RV pressure 56 mm Hg, LV pressure 59 mm Hg). These conditions might also be present in several of the patients in group III (pressure 41-60 mm Hg in RV), but this cannot be proved, as the pressure in LV was not measured.

Chapter IX

Treatment of the data in the present material of children with isolated VSD

With the help of I/S Datacentralen af 1959 (Ved Stadsgraven 15, København S), an attempt was made to elucidate somewhat more exactly the relationship between the pressure in the RV or PA and the magnitude of the left-to-right shunt, on the one hand, and on the other hand, a number of individual data from the clinical, roentgenological and electrocardiographic examination. The patient data are as follows: height, weight, age in months, length at birth, weight at birth, absolute volume of heart, relative volume of heart, cardiothoracic index (which was subsequently omitted from the final study), density of pulmonary vasculature on radiogram of thorax, as well as the following ECG values: electric axis, absolute height of RV_1 , SV_1 , RV_6 , SV_6 , RV_1/SV_1 , RV_6/SV_6 , RV_1+SV_6 and SV_1+RV_6).

The conclusion of the analyses carried out was that no major correlation could be demonstrated between the two catheterization data of pressure and shunt and the data recorded from the clinical, roentgenological and electrocardiographic examination at the first cardiological examination in 95 of the 124 children with isolated VSD under the age of 2 years at the time of the examination (not all the necessary data were available in 29 of the children). Thus, it is not possible with any acceptable degree of certainty, to make any statement as to the degree of severity of the condition isolated VSD, when the only data available are those from the clinical, roentgenological and electrocardiographic examination. Cardiac catheterization is therefore still a necessary procedure, if one wishes to make a statement as to the prognosis for the patient, and the possibility of a favourable outcome of any operative intervention, if this should be regarded as necessary in view of the patient's condition.

Chapter X

Medical treatment of isolated VSD

Review of the literature

There is agreement among the many authors with regard to indications for medical treatment of infants with isolated VSD (for literature and references see Ash 1964, Nadas 1964, Hoffman and Rudolph 1965, Lynfield et al. 1965, Taussig 1965, Nadas 1967). McNamara (1965) has provided a good review of the problems of pre- and post-operative medical treatment in corrective operation, and to a considerable extent this review can also be applied in the case of palliative operative treatment.

On the other hand, great differences are found in the results of the treatment. The mortality from purely medical treatment varies considerably, from very low values: Fyler et al. (1958): 1 out of 20, Lynfield et al. (1959a): 0 out of 9, Lynfield et al. (1965): 1 (4) out of 27, Hoffman and Rudolph (1965): 1 out of 62, up to rather high values, such as reported by Blount and Woodwark (1960): 9 out of 18 and Morgan et al. (1960): 10 out of 17.

Author's material

The medical treatment of the 124 children with VSD in the material, who were examined for the first time before the age of 2 years, during the period 1954 to 1963, naturally falls into 2 groups: 1) digitalis treatment (diuretics have practically not been used during the period from which the material originates), and 2) other medical treatment, including antibiotics, oxygen, opiates, ephedrine and theophyllamine preparations, postural drainage and toilette of the nasopharynx, over and above what has been employed prophylactically in car-

diac catheterization and prophylactically and therapeutically in the palliative operations. Furthermore, the treatment of diseases unrelated to the heart condition is likewise not included in this analysis.

It has been customary to put these ill cardiac children on a regimen consisting of more frequent, smaller meals than corresponds to the requirements of healthy children, possibly with feeding by tube over shorter or longer periods of time.

Digitalis treatment

Among digitalis preparations, "Tinct. digitalis" (1 ml = 56 drops, 1 drop = 1.8 mg digitalis) has been used since the beginning of the period of investigation, with a saturation dose under the age of 2 years of 33 mg/kg. From August 1962, the hospital changed over to using Digoxin (Digoxin paediatric elixir) with a saturation dose = 0.08 mg/kg for children under the age of 2 years.

Duration of the digitalis treatment: those children who died (operated on and not operated on) received digitalis up to death. In the case of the infants undergoing palliative surgery, the treatment lasted from 1 month (i.e. during and just after the operation) to 26 months. (Age at withdrawal: 3 months to 2 7/12 years). In the case of the children not operated on, from 1 month to 2 years (Age at withdrawal: 3 months to 2 9/12 years. However, in one of the children who was not followed-up, the time of withdrawal is not known).

Other medical treatment

Among antibiotics, penicillin preparations have been most used, but also sulphonamides, and more rarely tetracyclines. Oxygen has either been dosed via a glass funnel in front of the child's face or within an oxygen tent. Among opiates, guttae roseae (1 drop = 0.56 mg morphine) has been used (as almost the sole preparation), and the dosage has been 0.2 mg morphine per kg body weight. Further, ephedrine and theophyllamine preparations have been employed.

Based on the various forms of applied medical treatment, the material has been divided into 4 groups: digitalis-treated alone, medical treatment with the exception of digitalis, combined digitalis treatment and medical treatment, and a group consisting of non-medically treated, for comparison. These 4 groups have been correlated with the pressure in RV or PA and with the magnitude of the left-to-right shunt. As expected from previous studies of the material, the

various forms of treatment accumulate in patients with the high pressure, that lies in the neighbourhood of or equal to the pressure in the LV, while in relation to the various shunt sizes, the distribution is more scattered.

In reviewing the present material, it became obvious that digitalis treatment - in contrast to the other medical treatment - had been much less employed during the first of those years from which the material originates than in the later years, and for this reason the material was further divided into 2 groups: from the years 1954-1959, and the years 1960-1963, respectively. Examining each pressure group or shunt group, digitalis treatment as sole treatment has signified an improvement in the medical treatment results, with fewer deaths or patients operated on following an attempt at medical treatment, from the first to the second period of investigation, in the group with a pressure in the RV or PA ≥ 61 mm Hg and in the shunt groups with shunt sizes corresponding to oxygen saturation deficits in RV $\leq 9\%$ and oxygen saturation deficits in RV to RA = 10-19%. In the case of combined treatment with digitalis and other medical treatment, a corresponding improvement in the efficiency of treatment is found: during the first period, the combined treatment failed in all the 5 patients treated (2 in the pressure group 41-60 mm Hg and 3 in the pressure group ≥ 61 mm Hg, respectively, 1 in the shunt group 10-19% oxygen saturation deficit in RV to RA and 3 in the shunt group $\geq 20\%$). During the second period, 16 patients received treatment in the same manner. Here, the treatment failed in 9 (4 in the pressure group 41-60 mm Hg and 5 in the pressure group ≥ 61 mm Hg, respectively, and 1 in the shunt group 0-9% in oxygen saturation deficit in RV to RA, 6 in the shunt group 10-19% and 2 in the shunt group $\geq 20\%$), while the remaining 7 were able to survive with the treatment combination mentioned. With regard to the group not receiving medical treatment, it is most important to note that 13 children during the first period and 2 children during the second period, did not receive that chance from medical treatment which according to our present knowledge they should have had. In general, however, the employment and the efficiency of medical treatment have increased in the course of the period from which the material originates.

The fact that medical treatment, even in the better of the 2 periods, 1960-1963, has such a low relative efficiency (7 out of 16 who received medical treatment surviving on this, while the remaining 9 were either operated on or died), must also be considered from another point of view. Namely, that while the hospital has undoubtedly pursued a very efficient - although hardly efficient enough - regimen with regard to the medical treatment of these ill infants with VSD, the palliative, pulmonary artery constriction operation used in this age group represents in itself such a stress, especially for the RV, that it has been considered important not to carry the effort of medical treatment so far

that the final cardiac resources of the infant were used up, so that the infant was unable to survive the intervention represented by the palliative operation. As a result, the child has been referred for this operation a little earlier than it would have been if the medical treatment had been the sole therapeutic possibility. On the other hand, however, operation has been performed in some patients who might have been able to survive on the medical treatment alone.

Chapter XI

Surgical treatment of isolated VSD

Review of the literature

The ideal treatment of the disease condition isolated VSD is quite naturally closure of the septal defect, whereby the two circulations are separated, so that the condition in the patient becomes as in an individual with a normal heart. This, however, requires a radical operation with a high mortality in the youngest age groups.

Palliative operation

In recognition of the high mortality results which most operation teams have experienced as a result of the radical operation for VSD before the age of 2 years, especially in the case of the very ill patients under the age of 6 months, where the operation is a dire necessity if the child is to survive, many have used the procedure of operating in two stages. The first stage (with a single exception: Sirak and Hosier 1959, who created operatively an artificial ductus arteriosus), is an operation for pulmonary artery constriction, originally described by Muller and Dammann (1952a, 1952b) and later modified by Albert in 1958 (Albert et al. 1958, Fowler et al. 1958), then subsequently, when the child has become older, but not before the age of 3-5 years and most often later, the second stage, a corrective operation with cardiotomy.

Indication for palliative operation

The indications for carrying out the palliative operation of pulmonary artery constriction are that the infants should be under the age of 2 years, especially under the age of 6 months, they should have a large VSD with pulmonary hypertension and/or large - often very large - left-to-right shunt with high pulmonary blood flow, cardiac failure, partial or complete failure to thrive and recurrent pulmonary infection, and they should be so poorly as a result of their illness, that they cannot survive the first 2 years of life and in particular, as mentioned above, the first 6 months of life, on an efficient medical treatment (for literature and references see Hoffman and Rudolph 1965, Rokseth et al. 1965, Therkelsen 1965, Verney 1965, Verney et al. 1965, Westlake 1965, Gutheil 1966, Hallman et al. 1966, Schmitz and Wolf 1966, Smith et al. 1966, Higashino and Moss 1967, Husfeldt et al. 1967, Dammann and Carpenter 1968, Idriss et al. 1968, Therkelsen 1968). Only a couple of groups of authors oppose the "banding" procedure: Lynfield et al. (1965), Sigmann et al. (1967), or find that it is almost never necessary (O'Donovan et al. 1967).

Effect of the operation for pulmonary artery constriction (theoretical considerations)

The events which take place after the creation of the artificial pulmonary stenosis are on the one hand a reduction in the strongly increased pulmonary blood flow, whereby the strain on the left ventricle is reduced, together with an increase in the amount of blood directed into the greater circulation, and on the other hand more long-term results, namely that the histological vascular changes particularly in the pulmonary arterioles are hindered, or at any rate reduced in degree, so that they remain at a stage where the changes are reversible and not so pronounced, until a radical operation can take place. Bonham-Carter (1965) is of the opinion that the beneficial effect of the operation is due to an increased elasticity in the lungs, which can have an effect on both the cardiac failure and the pulmonary vascular resistance, as shown by the fall in the respiratory rate from before to after the operation.

Technique of the operation for pulmonary arterial constriction

The technique in creating the artificial pulmonary stenosis, as originally described by Muller and Dammann (1952a, 1952b), is that a portion of the main

branch of the pulmonary artery is resected, and around the narrowed part a band is applied which may, if necessary, constrict the region further, as a rule until a gradient of 50% is obtained between the pressure proximal to the stenosis and the pressure distal to the stenosis. This technique was later modified somewhat, retaining only the partial resection of the pulmonary artery, and omitting the application of the band around the stenosis, both so that the pulmonary stenosis applied should not be too narrow, and so that a gradual expansion of the stenosed region should be allowed following the growth of the child (Therkelsen et al. 1957, Therkelsen et al. 1959). A more radical modification was described by Albert (1958) (Albert et al. 1958, Fowler et al. 1958), who merely applied a band around the main branch of the pulmonary artery. This band was then tightened, until the desired stenosis was achieved. This modification (Dammann-Muller-Albert's operation) was supposed to possess two advantages over the original method: on the one hand give a more rapid and less risky operation, on the other hand presumably permit an easier reconstruction of the pulmonary artery in the case of a radical operation later in life. The gradient from proximal to distal to the stenosis varies in the reports on the patients by the various authors, from 10 to 65 mm Hg, or 20-79 % of the pressure proximal to the stenosis. For literature and references see Rokseth et al. (1965), Therkelsen (1965), Verney (1965), Hallman et al. (1966), Dammann and Carpenter (1968), Idriss et al. (1968).

Mortality

This palliative operation has been life-saving in many cases of severe VSD under the age of 2 years, especially under the age of 6 months, although the mortality is by no means small. Among other things, the mortality in the "banding" procedure depends to a high degree on whether the operational technique originally described by Muller and Dammann has been used (1952a, 1952b) (DM), the modification by Therkelsen et al. (1957 and 1959) (DM-modification), or the modified method of Albert (Albert et al. 1958, Fowler et al. 1958) (DMA). In those cases, therefore, where the method of operation has been described, the particular method employed will be mentioned in what follows. The immediate mortality, i. e. deaths during operation or in the course of the hospitalization during which the operation is carried out, are reported by various authors as follows: Muller and Dammann (1956), DM: 40%, Therkelsen (1956) DM: 50%, Therkelsen et al. (1959) DM: 50%, DM modified: 67%, DMA: 20%, Albert et al. (1961) DMA: 10%, Dammann et al. (1961) 33% (but not all were isolated VSD patients), Morrow and Braunwald (1961) DMA:

8%, Gammelgaard et al. (1962) DM + DM modified: 56%, DMA: 20%, Willmann et al. (1962) DMA: 8%, Ochsner et al. (1963) DMA: 0%, Cooley and Hallman (1964) DMA: 11% (the one patient who died, however, had an atrioventricularis communis defect), Fouron et al. (1964) 33%, Mustard (1964) DMA: 10%, Poulos et al. (1964) 0%, Verney et al. (1964) DMA: 33%, Goldblatt et al. (1965a) DMA: 20%, Goldblatt et al. (1965b) DMA: 20%, Lynfield et al. (1965) 14%, Rokseth et al. (1965) 16%, Sterns et al. (1965) 0%, Correa et al. (1966) DMA: 67%, Hallman et al. (1966) DMA: 15%, Smith et al. (1966) < 6 months: 45%, 6-24 months: 6%, Aberdeen and Waterston: < 5% (personal communication to Hollman 1967), Grainger et al. (1967): 40%, Hallman et al. (1967) DMA: 16%, Landtman et al. (1967): 29%, Nadas (1967): approx. 10%, Dammann and Carpenter (1968) DMA: < 6 months: 43.5%, 6-24 months: 5.6%, or in total: 26.8%, Idriss et al. (1968) 16%, Reid et al. (1968) 18 patients, of these 15 < 17 months old: 5.5%, Therkelsen (1968) $\leq$ 6 months DMA: 30%, Wada and Iwa (1969) DMA: < 1 year: 9%.

Complications

The procedure is not without complications, both early and late. Acute complications to the operation which have been described include haemorrhage at the site of resection when the operation is done by the method of Dammann-Muller and Dammann-Muller modified (Therkelsen et al. 1959), as well as frequent occurrence of respiratory failure and cardiac failure during the days immediately following the operation (Rokseth et al. 1965). Schmidt-Habelmann and Sebening (1966) have described two types of early post-operative complications: on the one hand the transection of the PA by the teflon band, with bleeding 10 days post-operatively, on the other hand transection of the PA by the endothelialized band without bleeding, 3 months after the operation, and Rohmer et al. (1967) have described 3 cases where the band had cut through the wall of the PA and lay in the lumen of the PA. Late complications include difficulties in removing the pulmonary stenosis formed at the later corrective operation (Lynfield et al. 1965, Gerard et al. 1966, Hallman et al. 1966, Sigmann et al. 1967). In contrast to this, Gammelgaard et al. (1961, 1962) have reported that when the band is applied by the "banding" procedure, it should be easy to remove, a view shared by Smith et al. (1966), although these claim, however, that plastic revision is often necessary. Nadas and Fyler (1968) report a risk of 5-10% in removing the band. A further late complication which has been described is the development of an obstructive hypertrophy in the infundibulum of the RV as a reaction to the pulmonary stenosis formed (Sigmann et al. 1967).

Idriss et al. (1968) find septicemia and infection as the most important complications. In addition, they describe 2 cases of transection of the PA by the band.

The clinical effect of the palliative operation

Those children surviving the operation improve strikingly, often after a rather critical period immediately following the operation. They flourish, thrive, emerge from their cardiac failure and lose their tachypnoea and the recurrent pulmonary infections (for literature and references see Schmidt-Habelmann and Sebening 1966, Schmitz and Wolf 1966, Grainger et al. 1967, Dammann and Carpenter 1968, Nadas and Fyler 1968). Their growth often becomes almost normalized, although not completely corresponding to their chronological age. However, at one time or another later in life (usually from the age of 3 to 8 years), cyanosis starts to develop, and the time has then come to perform a radical operation with closure of the septal defect and reconstruction of the pulmonary artery at the stenosed site. This reconstruction is reported by some investigators to be an increased risk factor in the radical operation (Lynfield et al. 1965), but others do not make this claim (Gammelgaard et al. 1961, 1962, Craig and Sirak 1963, Goldblatt et al. 1965b, Smith et al. 1966, Hallman et al. 1967). In the original Dammann-Muller operation and the modification without the band around the site of resection, the stenosed part of the pulmonary artery must be resected, which may increase the risk in the radical operation. In the Dammann-Muller-Albert modification, removal of the band will often leave a somewhat stenosed artery (quite apart from the fact that the band may have been so lodged in fibrous tissue that it may be very difficult to remove), and this will require a plastic operation on the artery (Goldblatt et al. 1965b, Hallman et al. 1966).

Author's material

Of the material of 144 children, including 124 under the age of 2 years at their first cardiological examination, a total of 41 were operated on (table 28); of these, 39 were examined for the first time cardilogically before the age of 2 years, by means of cardiac catheterization and possibly angiocardiography, while 2 (patients nos. 244 and 273) were not examined for the first time until the age of 10 years and 3 years 9 months, respectively.

Radical operations

A total of 8 primary radical operations were performed, 5 of them in direct association with or shortly after the first cardiological examination (patients nos. 35, 189, 207, 247 and 273), all of whom died, while 3 underwent a radical operation at a later stage (after the follow-up examination was carried out, but before the end of 1963). These 3 patients (nos. 37, 244 and 407) were 8, 14 and 4 years old, respectively, at the time of the operation. The radical operations will otherwise not be discussed or analyzed further, as on account of technical difficulties they were given up in 1957 in the case of infants with VSD who were under the age of 2 years.

Palliative operations

In the beginning of the period 1954-1963, the palliative operations were performed in Thoracic Surgery Department R, Rigshospitalet, and later on in the surgical department of the Queen Louise's Children's Hospital. The operators were Professor, dr. med. F. Therkelsen (F.Th.) Professor, dr. med. P. Gammelgaard (P.G.) and the late Physician-in-Chief, dr. med Thue Poulsen (Th.P.).

It might be mentioned here that part of the present material of patients has been published previously in studies by Therkelsen et al. (1957), Therkelsen et al. (1959), Gammelgaard et al. (1962), Therkelsen and Boesen (1962), Therkelsen (1965) and Husfeldt et al. (1967).

Course of the operation, mortality and causes of death

Tables 29a and 29b give a more detailed review of the conditions of the individual patients undergoing palliative operations. In connection with the actual operation. Table 29a comprises 9 patients operated on by the method of Dammann-Muller (5) and the method of Dammann-Muller modified (4); table 29b comprises 24 patients operated on by the method of Dammann-Muller-Albert.

The following 32 patients underwent palliative operation alone (+ after the number signifies that the patient died during or after the operation): nos. 2+, 5+, 10+, 16, 58, 68, 83+, 88+, 98+, 268, 276, 299+, 323, 335+, 338+, 353, 371, 381, 518, 542, 547+, 556, 571, 572, all from the period 1954-1960. In addition, from the period 1961-1963, when no follow-up examination took place: nos. 678+, 727, 728, 787, 858+, 864+, 871, 873+ (see table 29a and 29b). Of

Table 28. Surgical treatment in the 144 children with isolated VSD, both after the first cardiological examination and at a later stage. No palliative operations were performed after the age of 2 years. The patients who underwent palliative operation had a systolic pressure of from 48 to 85 mm Hg in the RV or PA on cardiac catheterization before the operation, and an oxygen saturation deficit from RV to RA of from 0 to 59%. (124 of the 144 children were under the age of 2 years at the first cardiological examination).

Type of palliative operation	Operation performed shortly after first exam. Number under/over 6 months at operation	died immed.	died after discharge	alive	operated on after follow-up, but before 31/12/63
Dammann-Muller	(<6 months: 2) 5 (≥6 months: 3)	0 3	0 0	2 0	
Dammann-Muller mod.	(<6 months: 2) 4 (≥6 months: 2)	2 1	0 0	0 1	
Dammann-Muller-Albert	(<6 months: 15) 24 (≥6 months: 9)	4 2	2 0	9 7	secondary radical operation; one (died)
total	(<6 months: 19) 33 (≥6 months: 14)	6 6	2 0	11 8	
Primary radical operation	5	5 ⁺)	0	0	3 ⁺⁺) (1 died)

+) one of these was over 2 years of age (4 years: pt. no. 273).
The other 4 were 6, 10, 14 and 19 months old at operation.

++) aged 4, 8 and 14 years (the 4-year-old patient died: pt. no. 407).

Tables 29a and 29b. These tables present the data of the palliative operations for pulmonary artery constriction. Table 29a shows the data for the 9 patients operated on by the method of Dammann-Muller or a modification (Dammann-Muller modificata), table 29b shows the data for 24 patients operated on by the method of Dammann-Muller-Albert.

No.	Name	Cath-eter, find-ings press./ shunt	Age at op. in. months	Died (days) after op. / alive	Place of operation and operator	Type of op. DM/ DM mod.	Pressure at start of operation				Pressure after resect.			
							RV	PA	LV	Aorta	RV	PA (dist.)	LV	Aorta
Table 29a														
2	J. A.	79/12	8	Died 3 days later	RH(R) F. Th.	D. -M.	47/9	50/23	50/10	50/34	45/13	43/17		
5	L. P.	81/45	12	Died on op. table	RH(R) F. Th.	D. -M.	No figures given, but it is reported that pressure in RV corresponded to that in PA and was 10 mm lower than in LV. Pressure in PA after resection: 25 mm Hg							
10	L. J. P.	52/13	23	Died 6 days later	RH(R) F. Th.	D. -M.	74/21	74/53	74/26	87/60	69/18	66/34	74/21	
16	B. R.	70/10	5	alive	RH(R) F. Th.	D. -M.	49/5	51/19	57/7	59/33	107/21	83/37	109/28	102/65
58	B. L. N.	74/52	5	alive	RH(R) F. Th.	D. M.	33/8	30/11 ↓ 56/26	26/5 ↓ 55/32	32/7	60/10 ↓ 76/13	42/17 ↓ 47/14		
68	B. R. N.	61/6	6	alive	RH(R) F. Th.	D. M. mod.	51/8	53/22	84/9		69/16	43/26	84/12	
83	B. T.	70/15	2	died 12 hours later	RH(R) F. Th.	D. M. mod.	37/4	34/16	47/6		23/4 (PA)	24/6		
88	K. M.	76/59	4	died 6 days later	RH(R) F. Th.	D. -M. mod.		43/30	55/33	57/46	76/54	60/52		
98	F. J.	67/30	8	died 4 days later	RH(R) F. Th.	D. -M. mod.	85/7	103/37	97/9	104/50	102/8	104/55	90/8	

P.A. diam. reduced to	Pressure after banding = final pressure				Remarks
	RV	PA	LV	Aorta	
	i mm Hg				
?	80/ 8	19 (mean)		81/ 50	Well 1½ days after op., then several attacks of unconsciousness, death 3 days after op.
¼		-			Died on op. table when Derras clamp was removed. Ligation not achieved.
½	87/ 26	77/ 51	90/ 24		- PDA. High diast. press. in RV. Myocard. failure. Preop. diag.: Suspected Eisenmenger's syndrome. For this reason only moderate narrowing. Cardiac action poor during clamping. Post-op.: Several resp. insuff. + signs of rt. -sided cardiac failure, death 6 days later.
¼- 1/5	97/ 20	67/ 36			Heart movement during clamping slower and incomplete, recovers. Further course uncomplicated.
?	70/ 8	25/ 12	77/ 12	77/ 47	PDA, without significance. Pressures at start of op. low due to hypotension in entire circulation, recovers.
?	68/ 3	35/ 20	71/ 9	73/ 45	Heart action poor during removal of a Derras clamp (fibrillation?) - recovered. No compl. post-op.
	(after further sutures)				
?	45/ 6	26/ 6			Heart action poor during free dissection of PA (heart massage, epinephrine, calcium) improvement, but with a-v block and flutter-fibrillation. PDA, without significance. Heart action poor: low pressure.
½	80/ 6	39/ 16	90/ 58		Condition good during op. 12 hrs later, atelectasis. 6 days later, unilateral cerebral symptoms, cyanosis, death.
/3	106/ 9	68/ 55			No PDA. Heart action poor, inadequate, with cyanosis of myocardium. Well at end of op., but 12 hrs later, clouded consciousness, poorly and with convulsions leading slowly to death. Pressure in PA could not be reduced further by making more sutures.

Table 29b.

No.	Name	Catheter. findings press. / shunt	Age at op. in months	Died (days) after op. / alive	Place of operation of and operator	Press. at start of operation	Pressure after banding of PA = final pressure mm Hg				PA diam. reduced to
							RV	PA	LV	Aorta	
268	H. B. H.	68/18	8	alive	DLB	?	syst.	syst.			?
					F. Th.		70	35			
269	O. M.	80/7	8	alive	DLB	?	86/7	50/15			?
					F. Th.						
276	T. H.	82/15	7	alive	DLB	?	Pressure periph. to the PS formed reduced to less than 2/3 of press. central to PS				?
					P. G.						
299	E. G. H.	69/11	5	died 18 days after op.	DLB	?	Pressure periph. to the PS formed reduced to less than 1/2 of the press. central to PS				?
					P. G.						
323	E. J.	70/19	3	alive	DLB	?	syst.	syst.			?
					F. Th.		70	40			
335	K. H.	68/8	9	died 5 days after op.	DLB	?	syst.	syst.			?
					F. Th.		80	60			
338	J. K. J.	80/37	5	died after discharge	DLB	?	Pressure periph. to the PS formed reduced to about 1/2 of the pressure central to PS				1/3
					P. G.						
353	K. L. P.	57/27	3	alive	DLB	?	Pressure periph. to the PS formed reduced to 20 mm Hg less than central to the PS				less than 1/2
					F. Th.						
371	K. J. A.	57/13	3	alive	DLB	?	syst.	syst.			?
					F. Th.		85	50			
381	S. E. J.	71/24	7	alive	DLB	?	syst.	syst.			more than 1/2
					P. G.		90	40			
518	K. R. J.	56/28	2	alive	DLB	?	syst.	syst.			?
					F. Th.		80	40			
542	S. S.	56/15	5	alive	DLB	?	syst.	syst.			?
					F. Th.		70-80	40			

Remarks

PDA, without signif. Cardiac action good during operation. Post-operative course without complications

Post-operative course uneventful

Heart rotated to right. Thymus enlarged. Post-op. course without complications

Cardiac arrest during op. at first attempt at narrowing of PA. Post-op. course very difficult with asthmatic respiration - tracheostomy, but condit. worsened steadily - death in presumed cardiac arrest

Cardiac action could not permit any further narrowing than that performed. Further course without complications

PDA 2 mm in thickness. Pt. could not tolerate further narrowing of the PA. Post-op. course without compl. until 48 hrs after op., when sudden resp. failure and cyanosis. Tracheostomy, but died in spite of manual ventilation and aspiration

PDA 6-7 mm long, few mm thick (no pressure change in PA on occlusion). Operation and post-op. course uneventful. Death from pneumonia after discharge

2 mm thick, 10 mm long PDA (no pressure change in aorta on occlusion). Diastolic pressure rather high, so PA was not narrowed further. Tachypnoea and cyanosis 24 hrs post-op. < tracheostomy, aspiration and manual ventil. Discharged well

Patient small, frail, with poss. of respiratory difficulties < tracheostomy. Condition fluctuating post-op., given manual ventilation. Subsequent course without compl.

Operation without complications, but post-op. pneumonia and atelectasis, although well on discharge

No complications during op. or post-operatively

No complications during op. or post-operatively

547	H. L.	48/20	5	died after discharge from hosp.	DLB F. Th.	?	syst. 90	syst. 60	?
556	U. W. J.	72/16	8	alive	DLB F. Th.	?	syst. 65	syst. 35	?
571	H. V. L.	78/18	7	alive	DLB F. Th.	?	syst. 70-80	syst. 35	?
572	M. C.	66/22	4	alive	DLB F. Th.	?	syst. 65	syst. 35	?
678	S. G.	80/30	3	died 2 days after op.	DLB F. Th.	?	syst. 70	syst. 50	?
727	A. L.	66/30	4	alive	DLB F. Th.	?	Pressure red. to half that of RV		?
728	G. S.	85/18	5	alive	DLB F. Th.	?	syst. 110	syst. 60	?
787	S. M. H.	79/12	6	alive	DLB F. Th.	?	syst. 70	syst. 40	?
858	H. N.	69/9	6	died 1 day after op.	DLB F. Th.	?	syst. 65	syst. 35	?
864	U. K. A.	78/0	2	died a few hours after op.	DLB Th. P.	?	syst. 100	syst. 40	?
871	B. K.	63/16	1	alive	DLB F. Th.	?	"pronounced gradient"		?
873	A. W. P.	60/13	4	died 15 days after op.	DLB F. Th.	?	syst. 75	syst. 40	?

Heart tolerated no more narrowing than performed (became blue and dilated). Postop. course difficult, failure to thrive. Did not start to thrive until 3 mths after op. Died from pneumonia 1 mth after discharge

Op. without complications, also the post-op. period (but uncertain whether op. improved condition)

Operation and post-op. course without complications

Cardiac action during op. somewhat unstable, but improved by the new press.grad. Disch. well

Cardiac action poor at start of op. Did not improve (and heart size did not decrease) as result of banding. Condition deteriorated, died 2 days later

Very thin PDA. Op. and post-op. conditions without complications

PDA 2 mm thick. Op. and post.-op. conditions without complications

Poor cardiac action repeatedly during free diss. of PA. No post.-op. complications

Cardiac action poor during banding attempt. Cardiac massage and injection of calcium chloride into LV necessary, and condition improves. Banding of PA now tolerated. PS-curve not obtained from pressure measurements in RV (presence of an infundibular chamber suspected). Condition satisfact. the first 12 hrs, then dies suddenly

Cardiac action good during op., but poor post.-op., with intermittent resp. and hemorrhage from pleural drain. Dies a few hours after op.

As the infant was very ill, the banding was not made so pronounced. Prolonged stormy postop. course with difficult resp. and cardiac decomp. Improved slowly

Operation without complications. General cond. post-op. characterized by inadequate coughing > aspiration. Later, infiltrations in both lungs > renewed aspiration and intubation. Did not improve > transferred to recovery ward, RH > died 15 days after op. (rupture of vessel wall)

Table 30. A group of patients who underwent palliative operation and a group not operated on, but with the same pressure characteristics in RV or PA, compared with regard to age of onset of first symptom, clinical and physical findings, radiological findings, electrocardiographic findings and pressure and shunt findings from the catheterization at first examination, to determine such possible differences in symptoms as might be decisive for the decision to operate or not.

In the entry "Ability to thrive in hospital", one patient has been omitted from the operated group and one from the group not operated on, because of inadequate information. The patient number in the entry "Relative volume of heart" has also had to be reduced to 26 operated on and 25 not operated on, and in the entry "ECG results" to 31 operated on and 26 not operated on, also because of inadequate information.

				operated on: 33		not operated on: 29	
				no.	no. of those dying (14)	no.	no. of those dying (3)
Anamnestic information	First symptom < 1 month			21	9	17	1
	"	"	1 "	5	2	3	0
	"	"	2-3 months	3	2	6	1
	"	"	4-5 "	4	1	0	0
	"	"	6-11 "	0	0	3	1
	"	"	≥ 12 "	0	0	0	0
Findings	x	Tachypnoea at rest		32	13	25	2
	x	Tachypnoea on effort		32	13	26	3
	x	Cyanosis at rest		6	4	3	1
	x	Cyanosis on effort		6	4	3	1
	x	Failure to thrive (≥ -10% of wt.)		29	13	23	2
		Failure to grow in length (≥ -10% of wt. for ht.)		18	7	15	2
		Voussure		17	7	15	2
		Thrill		3	1	8	0
		Systolic murmur		32	14	29	3
		Diastolic murmur		5	2	2	0
Physical and	x	Liver ≥ 1½ finger widths below costal margin		23	6	10	1
		Accent. of II sound		2	1	0	0
		Fingernail abnormalities		0	0	0	0
		No. of pts. who had					
		2 of the symptoms marked x		32		26	
	3	"	" " x	30		22	
	4	"	" " x	23		10	
	5	"	" " x	6		2	
	6	"	" " x	4		1	

Ability to thrive in hospital

≥ 99% of the normal for age 27 11 14 2

Table 30. contd.

				operated on: 33		not operated on: 29			
				no.	no. of those dying (14)	no.	no. of those dying (3)		
Radiological findings	Pattern of pulmonary vasculature normal = 0			0	0	1	0		
	sl. incr. = (+)			2	1	6	0		
	incr. = +			22	8	15	1		
	much incr. = ++			9	5	7	2		
	-----			-----		-----			
Radiological findings	Rel. heart vol.		≤ 399 ml	includes	2	1	9	0	
	"		" 400-499 ml	only	10	5	8	0	
	"		" 500-599 ml	26 op. on,	11	4	3	0	
	"		" ≥ 600 ml	25 not op. on at 1st exam.	3	1	5	1	
-----				-----		-----			
Electrocardiographic findings	Elec. axis normal, precord. lead normal			includes	0	0	4	0	
	"			" + LVH	only	0	0	0	0
	"			" + CVH	31	10	5	1	
	"			" + RVH	op. on	1	1	2	1
	LAD + norm. precord. lead			and	0	0	0	0	
	"			+ LVH	26	0	0	1	0
	"			+ CVH	not	6	2	4	0
	RAD + norm. precord. lead			op. on	0	0	1	0	
	"			+ CVH	at 1st exam.	10	2	6	0
	"			+ RVH		4	3	3	0
TV ₅ -V ₆ isoelect. to neg. (not digitalized)					8	3	1	0	
-----				-----		-----			
Catheterization findings from 1st exam.	Diagnosis VSD made solely on clinical findings + RG of heart + ECG				13	7	20	2	
	Oxygen deficit from RV to RA: 0-9%				5	3	5	1	
	"			" " " " " " : 10-19%		16	5	16	0
	"			" " " " " " : ≥ 20%		12	6	6	2
	Pressure in RA > 6 mm Hg				10	6	6	2	

the 12 dying within the post-operative period (3 weeks), one died during the operation; 2 died during the first day after the operation, 1 died 1 day after, 1 died 2 days after, 1 died 3 days after, 1 died 4 days after, 1 died 5 days after, 2 died 6 days after, 1 died 15 days after, and 1 died 18 days after. The causes of death were as follows: anoxia: 2, cardiac failure: 4, respiratory failure: 2, cardiac failure + respiratory failure: 3, transection of PA with hemorrhage caused by the band used to create the pulmonary stenosis: 1 (see tables 29a and 29b). The two patients dying later after return home from hospital, died 28 days after the operation and 4 1/2 months after the operation, in both cases from pneumonia (patients nos. 338 and 547). One patient (no. 269), as mentioned above, was operated on to begin with by the Dammann-Muller-Albert method, and later on underwent a radical operation. The material thus included a total of 33 infants under the age of 2 years who underwent palliative operation.

Indications for operation

In all the patients, the indications for palliative operation have been that the patients had pulmonary hypertension (most often severe, i. e. with a systolic pressure in the RV or PA ≥ 61 mm Hg, the same as or almost equal to the pressure in the LV; this holds for 26 of the 33 patients), and also varyingly great left-to-right shunts (this has often been found to be very great; in 12 of the 33 patients there was an oxygen saturation deficit in the RV-RA $\geq 20\%$), failure to thrive, tachypnoea, recurrent pulmonary infection and cardiac failure which could not be treated satisfactorily by drugs. To illustrate that it was the patients in the poorest condition who were selected for the palliative operation, the 33 patients in the operated group are compared in table 30 with a group of 29 patients who were not operated on, but who had the same pressure conditions in the RV or PA, i. e. all with a pressure greater than the lowest systolic pressure in the operated group. Apart from patient no. 547, with a systolic pressure of 48 mm Hg, but with a demonstrated pressure equalization with the LV, all the patients, both those operated on and those not operated on, had a systolic pressure ≥ 51 mm Hg in the RV or PA. The magnitude of the pressure in the RV or PA was chosen as the basis for selection for comparison between the two groups, as it has been shown repeatedly already in the present study that the pressure is the best single indicator of the patient's condition. The table shows the anamnestic data for the time of onset of the symptoms, the clinical and physical findings, whether the patient has been able to thrive in hospital, i. e. under optimum conditions, the results of the radiological

examinations as to the size of the heart and as to the intensity of the pattern of pulmonary vasculature, the electrocardiographic findings, and finally the magnitude of the left-to-right shunt between the ventricles and the magnitude of the pressure in the RA. In the column "increase in weight in hospital", patient no. 864 is omitted from those operated on and patient no. 379 from those not operated on, on account of inadequate information on increase in weight. Six of the patients not operated on are also omitted from the table: patient no. 297 (should have been operated on but died before operation), no. 401 (in whom operation was found indicated, but where the patient was found to be too old for the palliative operation), patients nos. 414 and 422 (whose condition was so poor that they should have been operated on, but where information on cyanosis led to the fear that the left-to-right shunt was about to reverse to a right-to-left shunt, and thereby cause the operation to be contra-indicated. This indication is somewhat unclear as to its basis, as other patients with resting and effort cyanosis have been referred for operation, but as the grounds have been included in the considerations: operation contra not operation, they have to be taken into account here), patient no. 467 (in whom operation was indicated, but who was too ill to take the risk of operation), and patient no 462 (who was so ill that death ensued before the question of operation was decided). Finally, in the column under "first cardiological examination" it was necessary to reduce the number of patients referred to under "relative volume of the heart" to 26 operated on and 25 not operated on, and in the column "ECG results" to 31 operated on and 26 not operated on, on account of inadequate information on the remaining patients. As mentioned on page 22, there were in all 6 spontaneous deaths in the material, but in table 30, only 3 of them have been included for the reasons mentioned above. These 3 deaths are in patients who were respectively 7 months old (no. 4), 3 months old (no. 262) and 3 months old (no. 297).

If now we compare the patients' columns at first examination for the patients not operated on and operated on, there is no special difference in the anamnestic information as to the time of onset of the disease. The same is the case in the temporary evaluation of the clinical and physical findings. If, however, we attempt to examine how many of the patients operated on or how many of the patients not operated on, had 2, 3, 4, 5 or 6 of the most important clinical and physical findings (here we ignore the systolic murmur, which was found in almost all), a clear preponderance of physical findings is seen in the group operated on. If we compare the ability to thrive in hospital, where this should enjoy optimum conditions, a correspondingly clear preponderance of lack of ability to thrive is found in those patients operated on, by comparison with those not operated on. With regard to the roentgenological symptoms, no

convincing difference is seen with regard to the intensity of the pattern of the pulmonary vasculature, whereas the difference is clear when it is a case of the relative volume of the heart: here there is a clear preponderance of cardiomegaly in those operated on, by comparison with those not operated on. With regard to the ECG results, the most striking difference between the two groups is the very great preponderance of signs of left-sided stress in the form of isoelectric to negative TV_5-V_6 in those operated on. Finally, it is interesting that the shunt conditions are almost the same in the two groups, just as are the pressure conditions in RA. Concluding, it may be said that the symptoms in those operated on and those not operated on have been rather uniformly represented in the case of many of the symptoms, but that the patients operated on have been in a poorer condition than those not operated on on 4 points: 1) with respect to the incidence of the combination of from 2 to 6 of the most important physical findings (tachypnoea at rest and on effort, cyanosis at rest and on effort, poor ability to thrive on admission to hospital and hepatomegaly), 2) poor ability to thrive in hospital in spite of optimum conditions for achieving maximum ability to do so, 3) cardiomegaly expressed by the relative volume of the heart, measured on the roentgenogram of the thorax, and finally 4) signs of left-sided cardiac loading on the ECG. The presence of these 4 symptoms or symptom groups has thus been a serious indication for referral of the patients for palliative operation.

As the two groups - those operated on and those not operated on - are thus not equally ill, although from a hemodynamic point of view they should be compatible, indication of the operational mortality (36%) (12 immediate deaths out of 33), by comparison with the spontaneous mortality (10%), is unfair, and cannot be ascribed any significance.

Time of operation

The time of operation is seen in table 29a and 29b: The age in months at which the palliative operation was performed varied from 1 month to 23 months with the following distribution: 1 month: 1, 2 months: 4, 3 months: 4, 4 months: 4, 5 months: 7, 6 months: 3, 7 months: 3, 8 months: 4, 9 months: 1, 12 months: 1 and 23 months: 1 patient. In other words, 29 out of the 33 patients were operated on in the period from 2 months of age to 8 months of age, which may presumably be explained by the fact that the worst period in the life of these infants - during which the operation was performed - is after the first few months of life, when the fetal pulmonary vascular resistance is still maintained, but before the 8th-9th month of life, when the reactive pulmonary vascular resistance has started to exert itself.

Operative mortality

The operative mortality (table 28) is high in the first two methods of operation: Dammann-Muller and Dammann-Muller modificata, with a total mortality of 60% and 75%, respectively. It might be mentioned that none of the patients died who were operated on by the Dammann-Muller method aged less than 6 months old, but in both types of operation the figures are too small for any weight to be attached to this observation. In the Dammann-Muller-Albert method, the number of patients is big enough to provide information of a certain weight, and here it is striking that there was almost no difference in the operational mortality between the group < 6 months of age and the group ≥ 6 months of age at the time of operation. According to the information in the literature, one might have expected a greater mortality in the first group, but on the other hand a much lower mortality in the second group. It is not possible to find any explanation for this state of affairs. The mortality with DMA was 25%.

Significance of the magnitude of the constriction

It was considered of some interest to attempt to relate the gradient created by the operation proximally to distally across the pulmonary stenosis, to the pre-operative catheterization findings, on the theory that a patient with pulmonary hypertension and a small left-to-right shunt, i. e. presumably a large vascular pulmonary resistance, should only be able to tolerate a considerably smaller gradient than the patient with the same tension in the PA, but with a large left-to-right shunt, i. e. presumably a slight vascular pulmonary resistance, so that the mortality should be greater in the first group than in the second group. However, it was not possible to find any evidence for this hypothesis in the present material.

Effect of the palliative operation

The immediate effect of the palliative operation has been a pronounced reduction in those symptoms which led to the indications for operation, even though it has been difficult for the patient to survive the first post-operative days, particularly on account of threatening respiratory failure and right-sided cardiac failure. However, the post-operative period in hospital has been too brief to allow the improvement to be measureable. It has been possible to note a

slight reduction in the rate of pulse and respiration, but the change has not been great, cf. a theory by Bonham-Carter (1965) on the effect of the operation, page . For that matter, the evaluation of the effect of the operation had to be put off to the follow-up examination, because it had to be assumed that a longer time was necessary than the few post-operative weeks (presumably a very much longer time) before it could be assumed that the pulmonary vessels, especially the pulmonary arterioles, had to a demonstrable degree become adjusted to the pulmonary stenosis taking over the function of a barrier against the high pulmonary blood flow and pressure, thus allowing the arterioles to regress to a more normal state.

Chapter XII

Histology of the pulmonary vessels and the significance of lung biopsy

Only a brief review will be given here of the findings in the histological studies of the lungs from 19 of the infants in the material (18 of them with pulmonary hypertension), all less than two years of age with one exception. Summarizing, it may be stated that the intimal changes found are very slight, that there is a clear thickening in the media in all vessels, and that in most cases the adventitia is clearly thickened. More severe changes were not found, and all the changes demonstrated are presumably reversible. This was to be expected, as with one exception the material examined only involved infants under the age of two years, an age group which should not show more severe vascular changes in the pulmonary tissue in pulmonary hypertension, especially not changes in the intima. Furthermore, it may be concluded that in these children with isolated VSD and pulmonary hypertension, measurements of the lumen and of the thickness of the vascular walls in the pulmonary vessels do not show any definite correlation with the size of the left-to-right shunt. Finally, it should be pointed out that operation biopsies (from the lingula pulmonis during operation for pulmonary artery constriction) are not representative of the more central regions of the lung tissue with regard to their vascular structure, as vascular changes in the lingula are less pronounced than the changes found in the autopsy preparations from the more central regions of the lung tissue (where an elucidation of the existing conditions is of greater importance), as has been emphasized by Therkelsen (1965), contrary to the opinions of Heath and Best (1958).

Chapter XIII

Follow-up examination

Review of the literature

A: Patients not receiving surgical treatment

General remarks on hemodynamic changes in isolated VSD after infancy:

Children with small VSD's and children with somewhat larger VSD's but only slightly elevated pulmonary artery pressure and not too large a left-to-right shunt, continued to do well as they grow older. However, most interest is attached to children with a large VSD and pulmonary hypertension, possibly pressure in RV or PA almost equal to or equal to the pressure in LV, and a varyingly large, in certain cases very large, left-to-right shunt, which has been demonstrated in infancy (for literature and references see Gasul et al. 1966, Edwards 1967, Dammann and Carpenter 1968).

After the first two years of life, these patients may undergo various spontaneous (i. e. non-surgically determined) developments from a hemodynamic point of view:

1. The hemodynamic conditions may improve, with stable pressure in the pulmonary circulation or possibly a fall in pressure and a decrease in the size of the left-to-right shunt. This may be due to one or more of the changes mentioned below (for literature and references see Gasul et al. 1966, Edwards 1967, Dammann and Carpenter 1968, Olin 1968).

a. Persistence of the general but reversible medial thickening in the lung arterioles with no special signs of irreversible intimal changes.

b. Relative reduction in the VSD, as the defect does not grow in step with the growth of the heart, and may not grow at all.

c. Gradual reduction in size, possibly total spontaneous closure of VSD.

d. Development of an infundibular stenosis in the outflow region of the RV, with subsequent fall in the size of the left-to-right shunt and in the pressure in the pulmonary circulation (but not in RV), possibly with conversion of the disease to a Fallot's tetralogy, when the stenosis becomes sufficiently pronounced (see page 102 for further details of this infundibular stenosis).

2. After the age of 2 years, the condition - untreated - may remain unchanged for many years (10-20), and then at the age of 20-30 years slowly exacerbate again on account of a progression in the changes in the pulmonary vasculature, which now terminate irreversibly in Eisenmenger's syndrome with death in right-sided cardiac failure (for literature and references see Ash 1964, Bloomfield 1964, Blount and Woodward 1960, Edwards 1967).

3. Already during the first few years of life, the condition may progress more or less rapidly because of the speed with which the changes progress in the pulmonary arterioles, with irreversible intimal changes developing quickly. On account of increasing pulmonary vascular resistance these changes lead to the development of a typical Eisenmenger's syndrome in the course of relatively few years (for literature and references see Kidd et al. 1965 b, Hoffman and Rudolfs 1966 b, Anderson et al. 1967). Kidd et al. (1965 b) demonstrated that those cases where a strongly increased pulmonary flow was present quite early in life were mainly those later developing progressive pulmonary vascular changes. Selzer and Laqueur (1951) described symptoms characterizing an Eisenmenger's syndrome (particularly cyanosis) in a group of 15 patients with isolated VSD. These symptoms were present already at birth or in infancy in 5 patients, in childhood in a further 5 patients and later in the remaining 5 patients. P. Wood (1958 a, 1958 b) reports that the tendency to subsequent development of Eisenmenger's syndrome is found at birth in 80% of the cases of Eisenmenger's syndrome described, which may be the final stage in the development of isolated VSD. Correspondingly, Bloomfield (1964) found that out of 14 patients with Eisenmenger's syndrome, 8 had been cyanotic from infancy.

Repeated catheterizations over many years

A number of authors have claimed that a large percentage of the patients examined show a rather rapid progressive hemodynamic development (in the course of just a few years, and even perhaps in the course of months) (for literature and references see Ritter et al. 1965, Hoffman and Rudolph 1966 b and Anderson et al. 1967).

Other investigators have found that the hemodynamic prognosis is less pes-

simistic in early infancy (for literature and references see Ash 1964, Bloomfield 1964, Blount and Woodward 1960, Kidd et al. 1965b).

Two problems will be discussed in a little more detail, namely the problems of partial or possibly total spontaneous closure of the VSD, and development of infundibular pulmonary stenosis in the outflow region of the RV.

I. Partial or total spontaneous closure of the VSD

Spontaneous closure of both membranous and muscular defects is most often found in patients during the first years of life and in those with small defects, but spontaneous closure may also be found in those with large defects, which have resulted in cardiac failure during the first years of life. The interval during which spontaneous closure most frequently takes place extends from the period around the first month of life up to the age of 6-7 years (more rarely first at puberty or even in adult life) (Agustsson et al. 1961, Agustsson et al. 1963, Wade and Wright 1963).

It has been demonstrated at autopsies that spontaneous closure of VSD may take place in various ways. There may apparently be a fibrous closure of the defect (Bloomfield 1961, Bloomfield 1964, Simmons et al. 1965, Suzuki and Lucas 1967), or there may be bacterial endocarditis, with secondary fibrosis as the main cause of the closure (Bloomfield 1961, Suzuki and Lucas 1967). There may be closure as a result of the septal leaflet of the tricuspid valve becoming firmly bound across the defect (Espino-Vela and Mata 1956, Majka et al. 1960, Bloomfield 1961, Albers et al. 1962, Miller and Kovachevich 1963, Sherman 1963, Bloomfield 1964, Simmons et al. 1965, Edwards 1967, Glancy and Roberts 1967), or there may be partial closure from the left side, either by the right cusp of the aortic valve, with increasing dilatation, arching in and prolapsing into the defect (although this results at the same time in the development of aortic insufficiency) (Nadas et al. 1964), or by the formation of an aneurism of the membranous part of the interventricular septum, so that the VSD is closed by the aneurism (Varghese et al. 1969, Misra et al. 1970). Finally, it is possible for a papillary muscle to adhere to the defect and close this, or the defect may be occluded by an infundibular stenosis in the outflow region in the RV (Vernant et al. 1963, Jain et al. 1969, Watson et al. 1969). The methods mentioned above apply primarily to the membranous defect, but it is believed that the purely muscular defect could close as a result of the muscular borders becoming adherent and finally growing together by fibrosis (Edwards 1967, Glancy and Roberts 1967).

Closure of a VSD has been reported clinically by a number of authors (for literature and references see Hollmann 1967, Nadas and Fyler 1968 and Olin 1968).

Spontaneous closure of a VSD, proven by cardiac catheterization, has by now been demonstrated by many investigators (for literature and references see Hoffman and Rudolph 1965, Kidd et al. 1965 a, 1965 b, Dammann and Carpenter 1968 and Nadas and Fyler 1968). Here, 3 cases of spontaneous closure of VSD should also be mentioned, proven by cardiac catheterization, following an earlier "banding" operation in the patients in question (Edgett et al. 1968, Nghiem et al. 1969, Stark et al. 1970).

Finally, some authors have found it necessary to assume indirectly that closure has taken place in the years following infancy, because of the discrepancy between the high number of VSD patients aged 2 years and the low number of VSD patients of adult age, since it is known that only very few patients with isolated VSD die during the period from the age of 2 years up to the 2nd - 3rd decade (Bloomfield 1964, Dammann and Carpenter 1968, Hoffman 1968, Nadas and Fyler 1968).

In general it may be said that small defects close spontaneously with greater facility than large defects, and on the whole, defects close more frequently during the neonatal period, but closure also occurs in older children and in adults. Bloomfield (1964) reports that in at least 25% of patients with small defects who survive infancy, the defect closes later in life. Hoffman and Rudolph (1966 a) report a figure of 36%, Olin (1968) 8-12%.

II. Development of infundibular pulmonary stenosis

In certain cases, an infundibular stenosis develops in the outflow region of the RV as a complication to isolated VSD. This infundibular stenosis, due to thickening of the muscle bundles in the crista supraventricularis and in the outflow region, has a favourable influence on the condition isolated VSD, at any rate to begin with, as it reduces the high pressure and the great flow to which the pulmonary circulation is exposed in the cases of large VSD. With time, however, the infundibular stenosis may progress, and in due course become so pronounced that the left-to-right shunt is converted to a right-to-left shunt, thereby presenting the picture of a typical Fallot's tetralogy (Gasul et al. 1957, Nadas 1957, Fyler et al. 1958, Lynfield et al. 1959 b, Dammann et al. 1960, Dammann and Carpenter 1968).

The frequency with which this obstruction develops in the outflow region of the RV in the case of isolated VSD is reported varyingly by different authors, from 40% (Gasul et al. 1957) to "about 5%" (Nadas and Fyler 1968).

Clinically, however, the development of an infundibular obstruction in the outflow region is difficult to distinguish from progressive peripheral vascular

changes in the pulmonary arterioles. The sole reliable diagnostic aid in this is cardiac catheterization with demonstration of a pressure gradient from the PA to the region just proximal to the pulmonary valve leaflets, and again from this "third chamber" (between the pulmonary ostium and the hypertrophic crista supraventricularis) to the RV (Dammann et al. 1960).

Clinical picture

The clinical course in those cases of isolated VSD not treated surgically has been described among others by Nadas (1957), Loogen (1958), Schaede et al. (1960), Veasy (1960), Lynfield et al. (1961), Ash (1964), Iverson et al. (1966) and Dammann and Carpenter (1968). Corresponding to the least severe type of isolated VSD, i. e. the condition with a small VSD, small left-to-right shunt and no pulmonary hypertension, the patients with this type continue a peaceful course from the first 2 years of life, and any mild symptoms such as slight retardation in growth and shortness of breath disappear. The systolic murmur may still be heard, but often decreases in strength, and its spread in the precordium decreases, just as the thrill decreases. There is no special accentuation of the pulmonary second sound. In many cases it is assumed that such a small VSD closes spontaneously, with the result that all the symptoms disappear. A patient with a somewhat larger VSD, but only slight pulmonary hypertension and moderate left-to-right shunt, likewise shows no great clinical changes after the age of 2 years, but the few symptoms such as retardation in growth and shortness of breath gradually disappear, and a stethoscopic examination shows that these patients continue to have a harsh, long, loud, systolic murmur along the lower left sternal border accompanied by thrill. In the course of some years, also this murmur may disappear, and together with it, the thrill.

On the contrary, in a patient with a large VSD, where the severe hemodynamic changes take place during the first 2 years of life, the clinical improvement which corresponds to the hemodynamic stabilization around the age of 2 years is particularly noticeable. In these at first very ill patients, an improvement is seen in all respects: they start to thrive and their growth becomes increasingly improved (although it is rare they reach completely the height and weight corresponding to their age), their shortness of breath - if due to stasis because of cardiac failure - decreases and disappears, and - what can be very striking - their tendency to recurrent pulmonary infections disappears almost completely. After the period around the age of 2 years, their mode of life may often be such as to approach that of a normal child, and it is only in exceptional

cases (those children in whom the hemodynamic conditions become steadily exacerbated right from infancy) that the improvement described does not appear. There is also a clear clinical improvement in those patients who develop an infundibular pulmonary stenosis, although this improvement is not always permanent.

Stethoscopic examination shows that the voussure is maintained, but the apex beat becomes less. The systolic murmur along the left sternal border becomes weaker, but harsh and shorter (and may even disappear). The pulmonary second sound increases in intensity. The diastolic flow murmur decreases slowly in intensity and may disappear. Among those patients developing infundibular pulmonary stenosis, there is a strong, harsh, systolic murmur along the upper left sternal border.

Corresponding to the hemodynamic conditions, this clinical improvement is usually maintained for many years, and extremely few patients with isolated VSD die from their heart disease between the age of 2 and 15-20 years (Harned et al. 1955, Gasul et al. 1957, Kaplan et al. 1961). In those cases, however, where the peripheral vascular pulmonary changes progress or where an infundibular pulmonary stenosis increases - and where a radical operation with closure of the defect is not performed - there develops at a certain point in the period between the end of the first decade and some time during the 2nd and 3rd decades, a change in the left-to-right shunt, which now becomes directed from right to left, resulting in reduced endurance, increasing dyspnoea, cyanosis and polycythemia with clubbing of the fingers and toes, and attacks of cerebral hypoxemia, together with a tendency to squatting (P. Wood 1958 a) (Eisenmenger's syndrome or Fallot's tetralogy). A stethoscopic examination shows that the systolic murmur decreases considerably in strength in Eisenmenger's syndrome, and may sometimes become systolic-diastolic, while the pulmonary second sound is strongly accentuated. The diastolic murmur is probably due to pulmonary valve insufficiency.

Radiology

The radiological changes will now be discussed (for literature and references see Iverson et al. 1966, Dammann and Carpenter 1968). After the first 2 years of life, a radiological examination of the thorax shows a normal unchanged picture in the case of the mildest forms of isolated VSD. A possible slight enlargement of the LV and a slight congestion of the pulmonary vessels disappears.

In addition, a slightly enlarged VSD, with moderate left-to-right shunt and only slightly increased pressure in the PA, tends in the direction of normalization of the thorax roentgenogram. In patients with VSD and a not particularly elevated pressure in the PA, but with a large left-to-right shunt, the congestion of the pulmonary vessels gradually decreases, just as the enlargement of LV and LA becomes less pronounced. In patients with a large VSD with pulmonary hypertension, possibly equalization between the ventricles and greater or lesser left-to-right shunt, there is from around the age of 2 years a gradual decrease in LV and LA, and the dilatation of the RV disappears (although the RV remains hypertrophic). The lung fields become more clear as a result of decreased congestion of the pulmonary vessels, apart from the perihilar vessels, which may still increase slowly in diameter (Capp et al. 1968, Simon 1968). The PA remains dilated, just as the aorta continues relatively small. In cases with the development of Eisenmenger's syndrome, the pulmonary vascular changes become in principle the same, except that the peripheral lung fields become quite clear, almost without any visible vessels and with a rather sudden transition to the central vascular regions with wide vessels, which increase in width proximally all the way up to the central, wide pulmonary vessels (Kjellberg et al. 1955, Hubbard et al. 1957, Weidman et al. 1963, Capp et al. 1968, Simon 1968). The enlargement of LV and LA disappears, but RV increases in size (however, the overall heart shadow most often decreases in size).

In the case of spontaneous closure of the VSD, the radiological picture of the thorax becomes normalized; if the patient develops a sufficiently large muscular obstruction in the outflow region in the RV, the diameter of the pulmonary vessels decreases in size both peripherally and centrally, but the heart changes observed radiologically correspond to what is seen in the development of Eisenmenger's syndrome.

Electrocardiography

The electrocardiogram is often an aid in evaluating the spontaneous temporal changes found in patients with VSD, whether in the direction of a normalization of the hemodynamic condition, or towards the development of either Eisenmenger's syndrome or Fallot's tetralogy.

The following changes may occur (for literature and references see Ash 1964, Bloomfield 1964, Dammann and Carpenter 1968): in patients with a small VSD and a small left-to-right shunt and no pulmonary hypertension, the ECG after the age of 2 years tends towards normalization. In patients with a somewhat larger VSD, with slight pulmonary hypertension and moderate left-

to-right shunt, the ECG continues to show left axis deviation and left ventricular hypertrophy, but the changes may decrease with time. In a VSD with slight to moderate pulmonary hypertension and a large left-to-right shunt, left axis deviation continues to be found, as well as left or combined ventricular hypertrophy. In a VSD with pulmonary hypertension and large or small left-to-right shunt, the ECG of which is characterized at an early stage by combined ventricular hypertrophy, the right ventricular hypertrophy may gradually increase (as a sign of slowly progressive vascular changes in the lungs) and the left ventricular hypertrophy decrease, so that finally the ECG often shows purely right characteristics (especially in cases with a small left-to-right shunt on account of high pulmonary vascular resistance). In Eisenmenger's syndrome, the ECG shows purely right ventricular hypertrophy and right axis deviation; the same is the case provided a considerable outflow-region obstruction develops in the RV. In spontaneous closure of the VSD, the ECG becomes normalized.

In patients with pulmonary hypertension and large or small left-to-right shunts, the rate at which the ECG may change from CVH to RVH is very important for the decision as to when the corrective operation should be carried out. It may be performed as long as there is still a definite sign of LVH in addition to the signs of RVH. Once the patient has reached the stage at which the ECG shows RVH exclusively, the operation involves risk (or at best is without any effect), and in Eisenmenger's syndrome it must be regarded as contra-indicated.

B: Patients undergoing palliative treatment by the pulmonary artery constriction operation:

Catherization studies after palliative operations

A few studies have been carried out on the hemodynamic conditions elucidated by cardiac catheterization following the procedure of artificial pulmonary stenosis (for literature and references see Fowler et al. 1958, McEachen and Smith 1960, Hallman et al. 1964, 1967, Takahashi et al. 1968). It appears from these studies that the pressure peripheral to the stenosis remains as measured at the time of the operation, or even falls further with time.

Clinical picture

The clinical effect of the pulmonary artery constriction operation is in contrast

to the hemodynamic effect described by numerous authors (for literature and references see Dammann and Carpenter 1968, Nadas and Fyler 1968, Takahashi et al. 1968, and Therkelsen 1968).

Those patients surviving the palliative operation and the rather severe post-operative period, improved clinically to a surprising degree; their general condition improves, they thrive, are no longer troubled by cardiac failure or respiratory tract symptoms such as tachypnoea and recurrent pulmonary infections. The improvement in their ability to thrive is seen both as an increase in weight and as an acceleration in length, but it is not always the case that these patients reach the mean value of weight-for-age and height-for age. A stethoscopic examination post-operatively shows that in the "pulmonary area" there is a harsh, loud, prolonged, systolic murmur, often accompanied by thrill.

After the improvement in the condition has been maintained for some years (2,5-8 years), increasing cardiac trouble again begins to develop (Therkelsen et al. 1959, Mills et al. 1960, Albert et al. 1961, Gammelgaard et al. 1961, Gammelgaard et al. 1962, Therkelsen and Boesen 1962, Therkelsen 1965, Smith et al. 1966, Nadas and Fyler 1968), with dyspnoea on effort and cyanosis on effort, inability to thrive and reduced endurance, cardiac insufficiency, dyspnoea at rest and cyanosis at rest with increasing polycythemia, indicating that the pulmonary stenosis originally constructed in the palliative operation remains unchanged during the growth of the child, and as a result has a relatively stronger effect in the course of the years. When the cyanosis becomes sufficiently pronounced, as a sign that a Fallot's tetralogy, partly artificially created, has now developed, the time has come for the second seance of the operative treatment of the isolated VSD: radical operation with closure of VSD and reestablishment of a normal, or at any rate more or less normal, pulmonary artery.

Different authors have reported a somewhat varying degree of improvement in the clinical condition following the palliative operation. The following have reported grades of improvement in the groups of the surviving patients and a classification according to the effect of the operation: Muller and Dammann (1956): excellent: 11/15, good: 3/15, poor: 1/15; Therkelsen et al. (1956): satisfactory: 1/3, considerably improved: 1/3, somewhat better: 1/3; Therkelsen et al. (1957): much better: 4/5, unchanged: 1/5; Fowler et al. (1958): considerably better 8/9; Therkelsen et al. (1959): excellent: 8/9, more or less satisfactory: 1/9; Gammelgaard et al. (1961); Gammelgaard et al. (1962); and Therkelsen and Boesen (1962): excellent: 10/12, somewhat better 2/12; Goldblatt et al. (1965 a): clearly improved 11/16, slight or no change: 5/16; Rokseth et al. (1965): pronounced improvement: 18/23, no

change: 5/23; Therkelsen (1965): excellent 12/15 (although 3 with late development of cyanosis), slight cardiac failure: 2/15, radical operation because of severe cyanosis: 1/15; Westlake (1965): good: 5/5; Correa et al. (1966): good: 4/5, complicated by thrombosis in PA: 1/5; Smith et al. (1966): < 6 months: all improved, 6-24 months: 94% improved; Landtman et al. (1967): good: 5/5; Therkelsen (1968): good: 14/15, severely cyanotic: 1/15.

The improvement following the pulmonary artery constriction operation appears within the first weeks or months after the operation (Therkelsen et al. 1959, Albert et al. 1961, Verney et al. 1964). Morrow and Braunwald (1961) and Goldblatt et al. (1965 b), however, report that the maximum effect of the operation does not appear until after 6-12 months have elapsed.

Radiology

The vascular congestion of the lungs is reduced, and the lungs may even develop a normal appearance; however, in a rather few cases they may also remain unchanged from their preoperative appearance (Therkelsen et al. 1957, Gammelgaard et al. 1961, Gammelgaard et al. 1962, Goldblatt et al. 1965 a, Gerard et al. 1966, Schmidt-Habelmann and Sebening 1966, Schmitz and Wolf 1966). Takahashi et al. (1968) found a pronounced reduction in the pulmonary vasculature post-operatively, namely in 87.5% of those patients in whom the PA pressure peripheral to the pulmonary stenosis had been reduced to 25% or more of the systemic pressure, but only in 53% of those in whom the "banding" had been less pronounced.

In the opinion of most investigators, the size of the heart decreases after the operation (Therkelsen et al. 1957, Gammelgaard et al. 1961, Gammelgaard et al. 1962, Bühlmeier et al. 1965, Schmidt-Habelmann and Sebening 1966, Schmitz and Wolf 1966). Takahashi et al. (1968) found that the transverse diameter of the heart was reduced post-operatively in only 14% of the patients, but found no correlation between the reduction in the size of the heart as determined radiologically and the degree of constriction of the PA achieved as a result of the operation.

Electrocardiography

In the electrocardiographic investigation, Gammelgaard et al. (1961), Bühlmeier et al. (1965) and Goldblatt et al. (1965 a) found that post-operatively there was an increased number of patients with signs of RVH. Takahashi et al.

(1968) found that the electric axis had changed from a mean value preoperatively of $+75.2^{\circ}$ to a post-operative value of $+100.4^{\circ}$.

Late complications

Late complications occur in the various types of narrowing of the pulmonary artery. In almost all cases, a plastic operation had to be carried out on the PA at the constricted part, in order to obtain even a reasonably good passage through this part of the vessel. Originally, it was expected that banding by means of the Dammann-Muller-Albert modification of the operation could be removed again on reoperation without any difficulty, and that the PA would then expand to a more or less normal size (Therkelsen et al. 1959, Gammelgaard et al. 1961, Morrow and Braunwald 1961, Gammelgaard et al. 1962, Craig and Sirak 1963), but this has hardly been the case. In most cases, the band disappears completely within fibrous tissue in the arterial wall and cannot be dissected free from this tissue. As a result, the constriction must as mentioned be considered and treated as a purely organic stenosis, and a plastic operation carried out on the PA (McEachen and Smith 1960, Goldblatt et al. 1965 b, Lynfield et al. 1965, Gerard et al. 1966, Hallman et al. 1966, Smith et al. 1966, Reid et al. 1968, Takahashi et al. 1968).

The time for a corrective operation after the "banding"

The time for the corrective operation in patients who have previously undergone a palliative operation is most often determined by the time when the left-to-right shunt reverses and becomes diverted from the right to the left, when the stenosis has become so narrow (relatively) that the pressure in the RV exceeds the pressure in the LV. From the point of view of age, this time will vary considerably, but usually lies between 3 and 10 years of age. The mortality in the corrective operation + "debanding" is usually reported as varying between 0 and about 1/3 of those operated on (McEachen and Smith 1960: 10%, Dammann et al. 1961: 4 out of 11 = 36%, Hallman et al. 1966: 1 out of 14 = 7%, Smith et al. 1966: 4 out of 11 = 36%, Hallman et al. 1967: 1 out of 23 = 4%, Dobell et al. 1968: 1 out of 16 = 6%, Nadas and Fyler 1968: 5-10%, Reid et al. 1968: 0 out of 2 = 0%, Wada and Iwa 1969: 1 out of 20 = 5%.

Incidence of neurological/mental disease in isolated VSD

The recording of these diseases often involves less difficulties in children older than those in the age group represented in particular at the first cardiological examination in the present material. On the other hand, a number of the cases of neurological disease and/or mental retardation have been excluded on a subsequent examination, because these conditions have been present in patients with such severe cases of isolated VSD that these patients have died in the course of the first years of life.

The neurological diseases in children with septal defects have been described by Tyler and Clark (1957, 1958): Incidence of loss of consciousness was 0%, of convulsions 3.6%, of brain abscesses 0.7%, of cerebral vascular insults 0%, and of mental retardation 2.6%.

Feldt et al. (1969 a) have examined the mental development in children over the age of 2 years with heart disease, and found that 9% among the acyanotic types were retarded. They found no correlation between the degree of severity of the heart disease and the results of the psychological examination. They mention in particular that among 103 children with VSD, there was no correlation between their IQ and the degree of severity of the disease, evaluated from the size of the left-to-right shunt, the presence and degree of severity of pulmonary vascular disease, or the occurrence of cardiac failure.

Author's material

Introduction

With the exception of one patient, all those patients who had not died (76), and who had undergone their first examination during the period from 1954 till the end of 1960, underwent a follow-up examination, the last one in 1964. The one exception was an Icelandic girl, with whom it had been impossible to come into contact in spite of repeated applications. There were thus altogether 75 patients who were followed-up. A number of these patients had been to control between the first cardiological examination and the follow-up examination, but these amounted to only 60% of the patients, so that any possible intermediate control examinations have been included in "the anamnesis up to the follow-up examination", i. e. the period from the first cardiological examination to the follow-up examination, just as in the case of the remaining 40% of the patients.

Of the 75 patients who were followed-up, 6 were followed-up by others than the author (1 in Greenland by the local physician, 3 in Iceland by Physician-in-Chief, dr. Tryggvason, 1 in the Pediatric Clinic of the Rigshospital

and 1 in the Cardiological Laboratory, the Aarhus Kommunehospital; the other 69 were followed-up by the author, either during readmission to hospital or as outpatients, most often called in for the purpose of a follow-up examination.

Figure 12 shows the age at the time of the follow-up examination of the 75 patients, as well as the sex distribution. In all cases the patients were over 2 years of age. Further, the figure shows the level of the pressure in RV or PA in the patients at the first cardiological examination, and how many of them had undergone palliative operation after the first examination (a total of 15, all under 2 years of age). Of the 75 children who were followed-up, 63 were under 2 years of age at first cardiological examination, and all these 63 were followed-up (the one who was not followed-up was more than 2 years of age at first examination).

The interval between the first cardiological examination and a follow-up examination was on the average $4\frac{1}{12}$ years (varying from $1\frac{8}{12}$ to $7\frac{5}{12}$ years) in the case of the 63 patients who were examined for the first time when under 2 years of age; in the case of the 12 patients who were examined for the first time when over the age of 2 years, the interval was on the average $3\frac{5}{12}$ years (varying from 2 years to $5\frac{9}{12}$ years).

At the follow-up examination, the subjective complaints of the children were reviewed, most often reported by the parents, immediately before and at the time when the follow-up examination took place, together with any possible information as to the course of the interval between the first cardiological examination and the follow-up examination ("anamnesis up to the follow-up examination"), as well as a clinical examination including weight and height measurements and a general cardiological examination, with a radiological examination of the thorax and an ECG.

Recatheterization was carried out in only 15 cases altogether. It would have been desirable if all the patients followed-up had undergone recatheterization, preferably in connection with the follow-up examination; however, it was not considered reasonable to subject these children to a further catheterization, as they were either too well to present the parents with a convincing argument that a further cardiac catheterization was motivated, or their condition was such that a further catheterization would presumably have been necessary in connection with a possible corrective operation. Even though the risk attached to a catheterization is small, it nevertheless does exist.

Recatheterization was carried out in 9 patients (nos. 23, 29, 47, 103, 119, 146, 238, 550 and 584) without any intervening surgical treatment, and in 6 patients (nos. 58, 68, 269, 323, 353 and 571) after surgical narrowing of the pulmonary artery had been performed. In 4 patients (nos. 29, 47, 58 and 68) angiocardiology was also performed; all those patients who underwent re-

catheterization were under 2 years of age at first cardiological examination. (See table 19, page 52).

With regard to the results of the few recatheterizations, it may be said in conclusion that the hemodynamic conditions in the patients who were not operated on were found to be unchanged in 3 of the patients (nos. 29, 47, and 238), improved in 4 of the patients (nos. 103, 119, 146 and 584), and worsened in one patient (no. 550), where the systolic pressure in the RV had increased so much that the left-to-right shunt would presumably reverse shortly after, so that there was no longer a possibility of corrective operation. (This patient thus belongs to the small group in whom the pulmonary vascular changes progressed with abnormal rapidity). In the case of the last patient (no. 23 BC), a hypertrophy of the musculature of the infundibulum must have developed between the two catheterizations, with the formation of a stenosis and a third chamber between the stenosis and the pulmonary ostium, resulting in a decrease in the load on the pulmonary circulation in the patient, and presumably a development towards a normalization of the pulmonary vessels. This probably explained why, in spite of the infundibular stenosis, the left-to-right shunt had increased to twice the value found at first catheterization. (For further details on this infundibular pulmonary stenosis, see page 102). In the case of the palliative operations, the results of the recatheterization showed that the operation had been successful in all those 5 cases where the examination could be carried through, while in one patient an evaluation could not be made on account of an incomplete examination.

The clinical picture at follow-up examination

Anamnestic symptoms at follow-up examination: These are shown in table 31 and table 32. However, it is obvious that there is no certainty that the hemodynamic conditions have remained unchanged from the first examination. The figures in brackets following the recorded figures give the incidence of the various symptoms in the same patients as the first cardiological examination.

In the case of the patients who were operated on, tables 31 and 32 show that failure to thrive, tachypnoea at rest (and to some degree also on effort), as well as cyanosis at rest and recurrent pulmonary infections, have decreased considerably from the first examination to the follow-up examination. The only anamnestic symptom which has increased at the follow-up examination is reduced endurance. In the case of the patients not operated on who have pulmonary hypertension, the tendency from the time of the first examination is in general seen to be the same as in the patients operated on; failure to thrive,

Fig. 12. Age distribution of the material's 75 children with isolated VSD who were followed-up, showing the sex distribution (45 girls and 30 boys). The pressure in the RV at first cardiological examination is also indicated, and whether a palliative operation was performed or not.

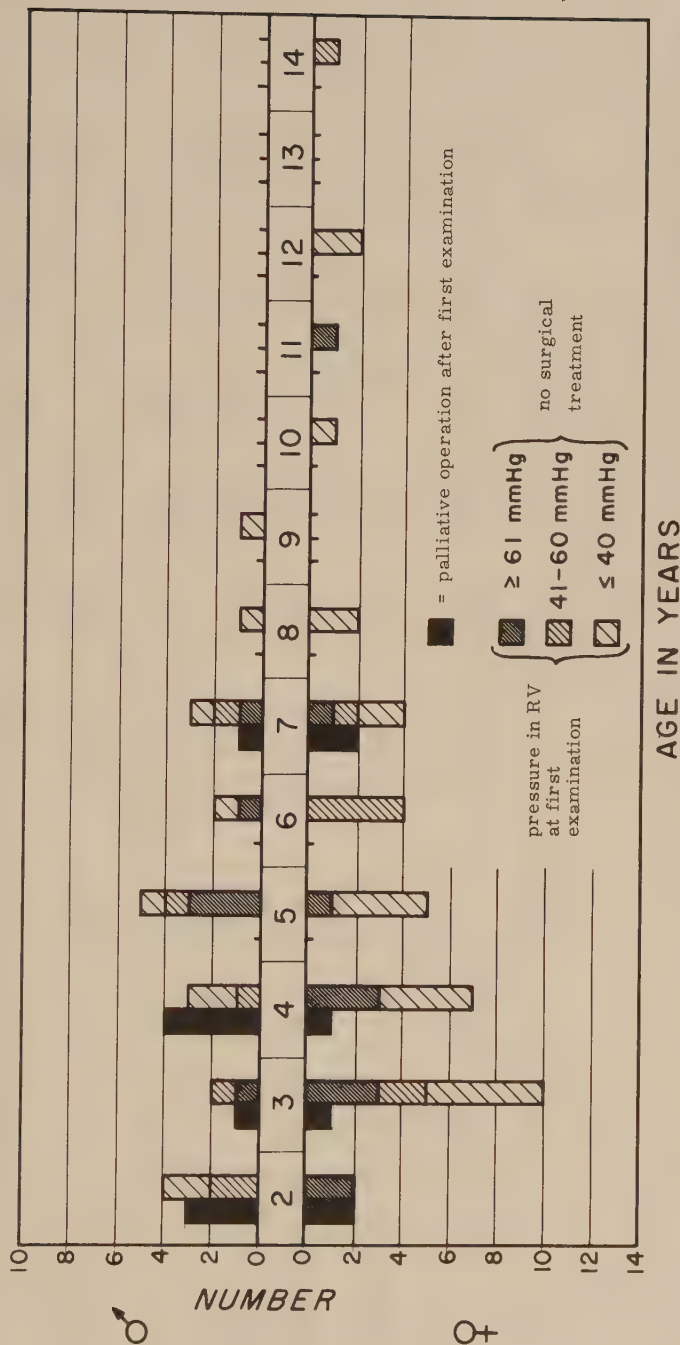


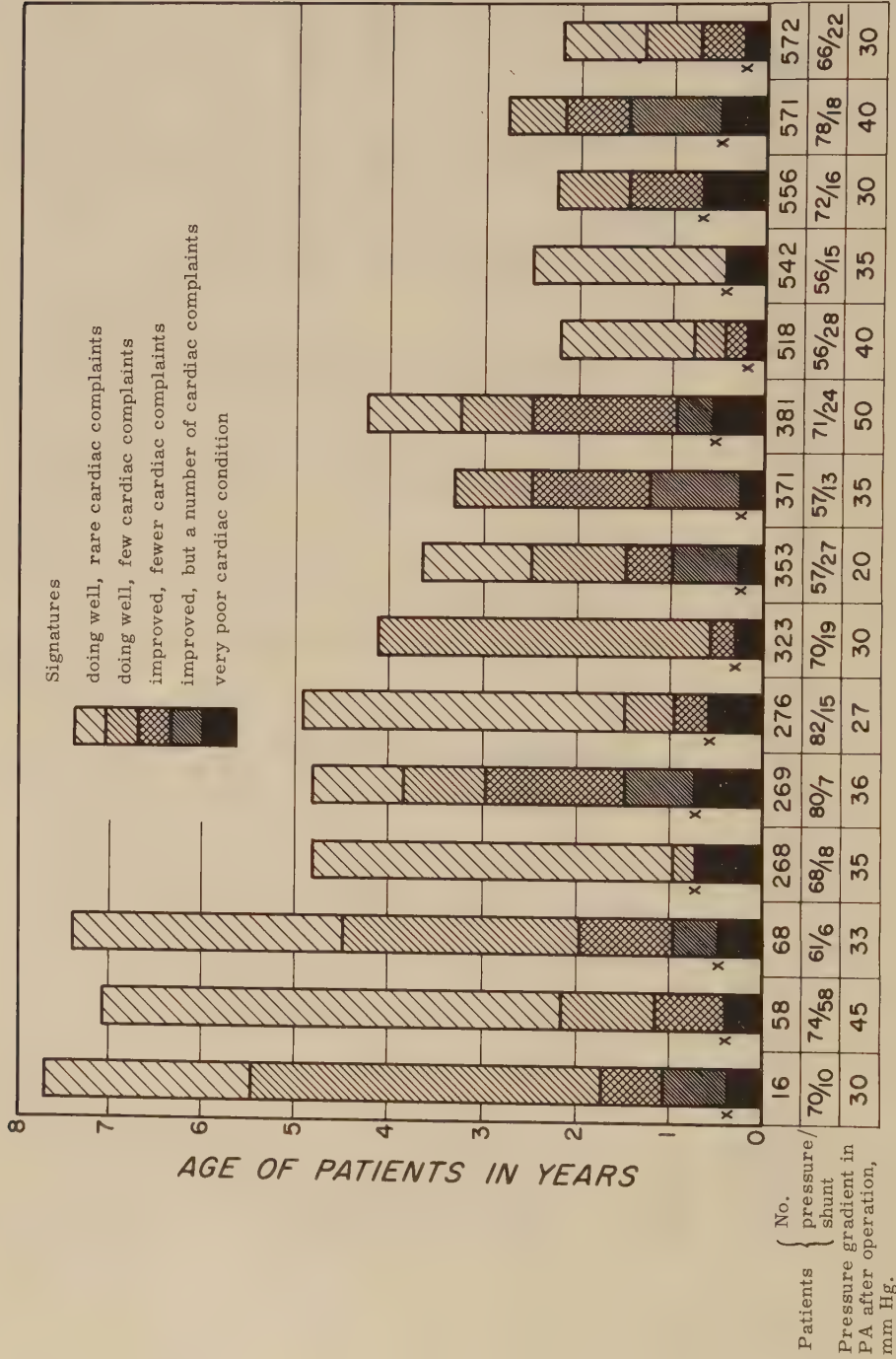
Table 31. The incidence of anamnestic symptoms at follow-up examination in 75 children with isolated VSD (including 63 under 2 years of age at first cardiological examination), in relation to the pressure in the right side of the heart at first cardiological examination. The figures in brackets give the incidence of symptoms at first examination.

Symptom	total		op. after 1st exam. all < 2 yrs	not operated on					
				< 40 mm		41 - 60 mm		≥ 61 mm	
	in all	< 2 yrs		in all	< 2 yrs	in all	< 2 yrs	in all	< 2 yrs
	75	63	15	29	21	14	13	17	14
Failure to thrive	5(43)	5(39)	2(11)	0(12)	0(10)	0(6)	0(6)	3(14)	3(12)
Tachypnoea at rest	7(21)	7(21)	1(8)	2(3)	2(3)	3(5)	3(5)	1(5)	1(5)
Tachypnoea on effort	34(37)	28(33)	9(11)	11(8)	8(5)	7(8)	6(8)	7(10)	5(9)
Cyanosis at rest	1(1)	1(1)	0(1)	0(0)	0(0)	0(0)	0(0)	1(0)	1(0)
Cyanosis on effort	10(19)	9(17)	4(4)	3(1)	2(1)	2(7)	2(7)	1(7)	1(6)
Reduced endurance	25(9)	22(7)	4(1)	12(5)	10(3)	4(0)	4(0)	5(3)	4(3)
Recurrent pulm. infect.	5(20)	5(19)	0(7)	2(5)	2(4)	1(2)	1(2)	2(6)	2(6)

Table 32. The incidence of anamnestic symptoms at follow-up examination in 75 children with isolated VSD (including 63 under 2 years of age at first cardiologial examination), in relation to the left-to-right shunt at first cardiologial examination. The figures in brackets give the incidence of symptoms at first examination.

Symptom	total in all 75	op. after 1st exam. all < 2 yrs 15	not operated on				
			0 - 9 % in all 17	< 2 yrs 11	10 - 19% in all 26	< 2 yrs 21	≥ 20% in all 17 < 2 yrs 16
Failure to thrive	5(43)	5(39)	2(11)	0(7)	2(14)	2(12)	1(10)
Tachypnoea at rest	7(21)	7(21)	1(8)	1(1)	3(5)	3(5)	2(7)
Tachypnoea on effort	34(37)	28(33)	9(11)	3(4)	15(11)	11(8)	6(10)
Cyanosis at rest	10(19)	9(17)	4(4)	0(3)	3(1)	2(6)	3(5)
Reduced endurance	25(9)	22(7)	4(1)	5(2)	9(1)	7(1)	6(3)
Recurrent pulm. infect.	5(20)	5(19)	0(7)	1(1)	3(7)	3(7)	1(3)

Fig. 13. Evaluation by the parents (graduated according to the signatures), at the time of the outpatient examinations, of the condition of the patients from time of operation (marked with x) to the time of follow-up examination (when the column terminates), in 15 patients who underwent palliative operations, and who survived with VSD with pulmonary hypertension, all patients having undergone cardiological examination and palliative operation before the age of 2 years. Cardiac complaints comprise: tachypnoea, recurrent symptoms from respiratory tract, reduced endurance and signs of cardiac insufficiency.



tachypnoea at rest and also on effort and recurrent pulmonary infections, have all decreased considerably. Likewise, as in the case of those operated on, there is an increase in the number with reduced endurance. Only on one decisive point is there a difference between those operated on and those not operated on, namely with respect to "cyanosis on effort", which is most frequent in the group of those operated on. This must be ascribed to the artificially created pulmonary stenosis; the hearts in the patients operated on have been converted to "acyanotic Fallot's tetralogy", with a tendency for the shunt to reverse on effort. In the group of those not operated on who had a systolic pressure in RV or PA $\bar{\leq}$ 40 mm Hg, the same tendency is seen as in the other group; here too, the symptom of reduced endurance has increased, but presumably the reason for this is that when the mobility of the infant increases with increasing age, and the general condition of the infant improves, symptoms such as reduced endurance will be recorded more frequently. If a follow-up comparison is made between those operated on and those not operated on, the latter divided into groups according to various shunt sizes at first catheterization, the same tendency is reflected as was found above for the groups with the various pressures.

The anamnestic symptoms from the first cardiological examination to the follow-up examination ("The anamnesis up to the follow-up examination")

However, tables 31 and 32 above all presumably provide a picture of how the parents of the patients have interpreted the condition of the children during the period immediately before the follow-up examination. In order to obtain an impression of how the patients - grouped according to various pressures in RV or PA at first examination - have developed right from the first cardiological examination to the time of the follow-up examination, the anamnesis has been reviewed in each patient to the extent that information has been available on the conditions between the first examination and the follow-up examination (possibly together with the results of interim outpatient control examinations as a support). These results have been grouped as follows: for those patients who were under the age of 2 years at first examination (a total of 63): groups 1-5, and for those who were over the age of 2 years (12): group 6.

1. Patients not operated on, with a systolic pressure in RV or PA $\bar{\leq}$ 25 mm Hg at first examination. Of these 8 patients, 7 had no cardiac complaints whatever during the period between the first examination and the follow-up examination. Only one (no. 496) reported having had slight difficulty in tolerating more severe efforts.

2. Patients not operated on, with a systolic pressure in RV or PA = 26-40 mm Hg at first examination: 7 out of the 13 patients had no cardiac complaints whatever. In the case of the other 6, the complaints were: reduced endurance in 5, more rapid shortness of breath on effort in 3, tendency to bronchitis or pneumonia in 3.

3. Patients not operated on, with a systolic pressure in RV or PA = 41-60 mm Hg at first examination: 5 of these 13 patients had no cardiac complaints whatever between the first examination and the follow-up examination (NB: including patient no. 550 mentioned previously, who on recatheterization after the follow-up examination was found to have developed severe hemodynamic changes, presumably caused by progressive changes in the pulmonary vessels with a high systolic pressure in RV or PA and decreasing size of left-to-right shunt). Up to the age of 2-2 1/2 years, 2 of the 13 patients had a slight tendency to bronchitis or pneumonia, to thriving poorly, and to becoming tired and short of breath more rapidly. Since then and up to the time of the follow-up examination, there has been no subjective cardiac complaints. In the case of the last 6 patients, the complaints were as follows: more rapidly tired than those of the same age: 3 patients, shortness of breath at rest: 3 patients, more rapid shortness of breath on effort: 6 patients, tendency to bronchitis or pneumonia: 3 patients, tendency to cyanosis on effort: 2 patients.

4. Patients not operated on, with a systolic pressure in RV or PA $\geq$ 61 mm Hg on first examination: None of these 14 patients have been completely free from cardiac complaints during the period between the first examination and the follow-up examination. 7 of these 14 patients, however, had been almost completely well already from the start of the period; their complaints were as follows: more rapidly tired than those of the same age: 3 patients, shortness of breath on effort: 7 patients, tendency to bronchitis or pneumonia: 1 patient, thriving poorly: 1 patient. Four of the remaining 7 patients had cardiac discomfort during the first period, but they improved slowly during the period between 1 and 2 1/2 years, after which their condition was clearly more stable. Their complaints were as follows: tired more rapidly than those of the same age: 2 patients, more rapid shortness of breath on effort: 2 patients, tendency to bronchitis or pneumonia: 2 patients. The last 3 patients of this group had almost permanently severe cardiac complaints, although the disease decreased somewhat with increasing age. The complaints in these 3 patients were as follows: more rapidly tired than those of the same age: 2 patients, shortness of breath at rest: 2 patients, more rapid shortness of breath on effort: 3 patients, tendency to bronchitis or pneumonia: 3 patients, thriving poorly: 3 patients.

5. Patients who underwent palliative operations: All 15 patients improved after the palliative operation, but not equally quickly, and the improvement was not

equally pronounced in all. The complaints were the same as those mentioned as most frequent in the group of patients not operated on, with severe pulmonary hypertension: reduced endurance, tendency to shortness of breath, particularly on effort, tendency to bronchitis or pneumonia, thriving poorly, and as something special for this group, a certain tendency to cyanosis on effort. However, the changes in the incidence of the symptoms and in the degree of severity took place more rapidly in this group than in the untreated patient groups, so that an attempt has been made graphically in fig. 13 to indicate the evaluation of the parents as to the condition of the child from birth to the time of the palliative operation and up to the time of the follow-up examination. The transitions are marked as well as could be estimated from the case records. The lower line of figure 13 shows the pressure gradient in mm Hg which was obtained as a result of the stenosis formed in the PA, to see whether there was any correlation between the magnitude of the gradient and the degree of improvement after the operation. No such correlation could be demonstrated. The two patients with the greatest pressure gradient after the operation were among those who had the most severe post-operative period. The patient with the lowest gradient had a milder post-operative period, but not strikingly better than patients with higher gradient.

With regard to the value of the palliative operation, i. e. the factor deciding when it is time for the corrective operation, the occurrence of cyanosis at rest is an important sign, which indicates that the pulmonary stenosis has now increased so much, relatively and perhaps absolutely, that the left-to-right shunt is about to reverse to a right-to-left shunt. This sign of cyanosis has been reported by the parents of 4 of the 15 patients aged respectively 7 1/12 (no. 58), 4 10/12 years (no. 269), 4 11/12 years (no. 276), and 4 1/12 years (no. 323). 2 of these had slight polycythemia, while the other 2 had normal hemoglobin values (with normal colour index).

Late complications to the palliative operation were not found in the present material.

6. Patients not operated on, with isolated VSD, examined for the first time after the age of 2 years (8 with systolic pressure in RV or PA $\bar{\leq}$ 40 mm Hg, 4 with pulmonary hypertension and systolic pressure in RV or PA from 48 to 94 mm Hg): Of the 8 patients without pulmonary hypertension, 5 had no cardiac complaints whatever between the first examination and the follow-up examination, while 3 had had milder symptoms: shortness of breath on effort: 3 patients, more rapidly tired than those of the same age: 2 patients, or pain in the precordium on effort: 1 patient. Of the 4 patients with pulmonary hypertension, 1 had had no cardiac complaints whatever between the first examination and the follow-up examination, while 3 had had mild cardiac complaints: slight shortness of breath on effort.

Clinical and physical findings on follow-up examination

The clinical and physical findings on follow-up examination are indicated in tables 33 and 34. These tables show that among those operated on, the sole symptom which has decreased with certainty is tachypnoea at rest. The observation that voussure and thrill have increased, is presumably associated with the fact that both symptoms do not occur particularly frequently at birth and during the first months of life, and increase in strength only slowly. In the case of those patients not operated on, who had pulmonary hypertension on first examination (i.e. systolic pressure in RV or PA ≥ 41 mm Hg), and who should be more or less comparable with those patients operated on, it is also the case that tachypnoea at rest is the sole symptom which has clearly decreased in incidence.

A number of the separate clinical findings in the follow-up examination will now be reviewed.

Ability to thrive

Weight (both weight-for-height and weight-for-age) showed that for both values, but especially in the case of weight-for-age, there was a clear dependence on the pressure in RV or PA (measured at first examination). The lower the pressure, the more patients achieved a normal weight by the time of the follow-up examination, while the higher the pressure at first examination, the fewer reached a normal weight by the follow-up examination, ignoring the difference - which was rather slight - in the numbers with normal weight and too low weight in the three "pressure groups" at first examination (< 40 mm Hg, 41-60 mm Hg and ≥ 61 mm Hg in RV or PA). The same tendency was found in the case of those who had undergone palliative operation (here, all the patients had had hypertension at first examination). The change in weight showed an even more pronounced dependence on the absence or presence of pulmonary hypertension. In the patients without pulmonary hypertension, 82% showed a tendency to a relative increase in weight from the first to the second examination, while 12% showed a tendency to a relative fall in weight; in the patients with pulmonary hypertension, a tendency to a relative increase in weight was shown in weight was shown in only 57-64% of those not operated on and in 50% of those operated on, while a tendency to a relative fall in weight was shown in 43-36% of those not operated on and in 50% of those operated on. In a group of 15 operated on and 17 not operated on (with the same systolic pressure in RV or PA at first examination as those operated on), a comparison

Table 33. The incidence of the clinical and physical findings at follow-up examination in 75 children with isolated VSD (including 63 under 2 years of age at first cardiological examination), in relation to the pressure in the right ventricle at first cardiological examination. The figures in brackets give the incidence of the findings at first examination.

Symptom	total in all 75	op. after 1st exam. all < 2 yrs 15	not operated on					
			≤ 40 mm		41 - 60 mm		≥ 61 mm	
			in all 29	< 2 yrs 21	in all 14	< 2 yrs 13	in all 17	< 2 yrs 14
Tachypnoea at rest	5(43)	5(41)	2(15)	0(7)	1(8)	1(8)	2(13)	2(12)
Cyanosis at rest	7(3)	6(3)	2(1)	0(0)	0(1)	0(1)	5(1)	4(1)
Failure to thrive	43(55)	37(46)	11(12)	9(17)	6(13)	8(11)	15(14)	12(1)
Poor growth	27(35)	24(31)	10(8)	3(11)	2(9)	5(7)	9(9)	8(7)
Voussure	46(21)	40(20)	13(7)	12(1)	10(1)	8(2)	13(11)	10(10)
Thrill	53(28)	49(21)	13(2)	17(13)	15(9)	10(5)	13(8)	12(5)
Systolic murmur	74(74)	62(62)	15(14)	28(29)	20(21)	14(14)	13(13)	17(17)
Diastolic murmur	8(10)	5(5)	0(3)	3(3)	1(1)	2(2)	1(1)	3(0)
Closure of defect	1	1	0	1	1	0	0	0
Mental retardation	5	5	1	2	1	1	1	1

Table 34. The incidence of the clinical and physical findings at follow-up examination in 75 children with isolated VSD (including 63 under 2 years of age at first cardiological examination), in relation to the left-to-right shunt at first cardiological examination. The figures in brackets give the incidence of the findings at first examination.

Symptom	total		op. after 1st exam. all < 2 yrs 15	not operated on					
	in all 75	< 2 yrs 63		0 - 9% < 2 yrs		10 - 19% < 2 yrs		≥ 20% < 2 yrs	
				in all 17	11	in all 26	21	in all 17	16
Tachypnoea at rest	5(43)	5(41)	2(15)	0(1)	0(1)	1(17)	1(16)	2(10)	2(9)
Cyanosis at rest	7(3)	6(3)	2(1)	1(1)	1(1)	3(1)	2(1)	1(0)	1(0)
Failure to thrive	43(55)	37(46)	11(12)	9(10)	6(7)	12(19)	10(15)	11(13)	10(12)
Poor growth	27(35)	2(31)	10(8)	5(5)	4(4)	8(12)	7(10)	4(10)	3(9)
Voussure	46(21)	40(20)	13(7)	5(2)	4(2)	20(8)	16(7)	8(4)	7(4)
Thrill	53(28)	49(21)	13(2)	9(6)	8(4)	19(10)	17(6)	12(10)	11(9)
Systolic murmur	74(74)	62(62)	15(14)	16(17)	10(11)	26(26)	21(21)	17(17)	16(16)
Diastolic murmur	8(10)	5(5)	0(3)	2(2)	1(1)	4(3)	2(0)	2(2)	2(1)
Closure of defect	1	1	0	0	0	1	1	0	0
Mental retardation	5	5	1	2	2	1	1	1	1

between weight-for-height and weight-for-age showed no certain difference. It should be added, however, that the group of those operated on were originally in a poorer condition clinically than those not operated on, so that in fact the comparison is really more to the advantage of the group of those operated on. In the patients with pulmonary hypertension who were not operated on, a classification according to size of shunt (at first examination) or according to the value of the pulmonary vascular resistance (fig. 14) shows that it is the patients with the small shunts (corresponding to a high pulmonary vascular resistance) who continue to thrive poorly, while the patients with large shunt values (lower pulmonary vascular resistance) show a tendency to thrive better with time.

Height at the follow-up examination tends to become normalized in relation to the first examination, but the differences are small.

Tachypnoea

The incidence of tachypnoea has definitely decreased, both among those patients operated on and those patients not operated on. In the patients who were operated on, it was present in only two patients at the follow-up examination, but present in all 15 at first cardiological examination. Among the patients who were not operated on, the incidence of tachypnoea had also decreased considerably from the first examination to the follow-up examination, in all groups of pressure values and shunt sizes (measured at the first cardiological examination).

Cyanosis

The 5 patients who were cyanotic at follow-up examination had at the first cardiological examination a systolic pressure in RV or PA, in mm Hg, and a left-to-right shunt expressed by the oxygen saturation deficit RV to RA in %, as follows: no. 29: 76 mm Hg/33%, no. 214: 94 mm Hg/11%, no. 277: 86 mm Hg/15%, no. 334: 79 mm Hg/8% and no. 422: 68 mm Hg/13%. Thus, all 5 patients had a severely increased systolic pressure in RV or PA equal or almost equal to the pressure in the LV, and apart from no. 29, no strikingly large left-to-right shunt. There is thus no support for the assumption by Kidd et al. (1965 b), that it was particularly patients with a large pulmonary flow quite early in life, who later developed progressive lung changes (see page 100). It may be assumed that between the first examination and the follow-up examin-

ation, these patients had developed an Eisenmenger's syndrome (without the possibility of operative treatment), or a Fallot's tetralogy.

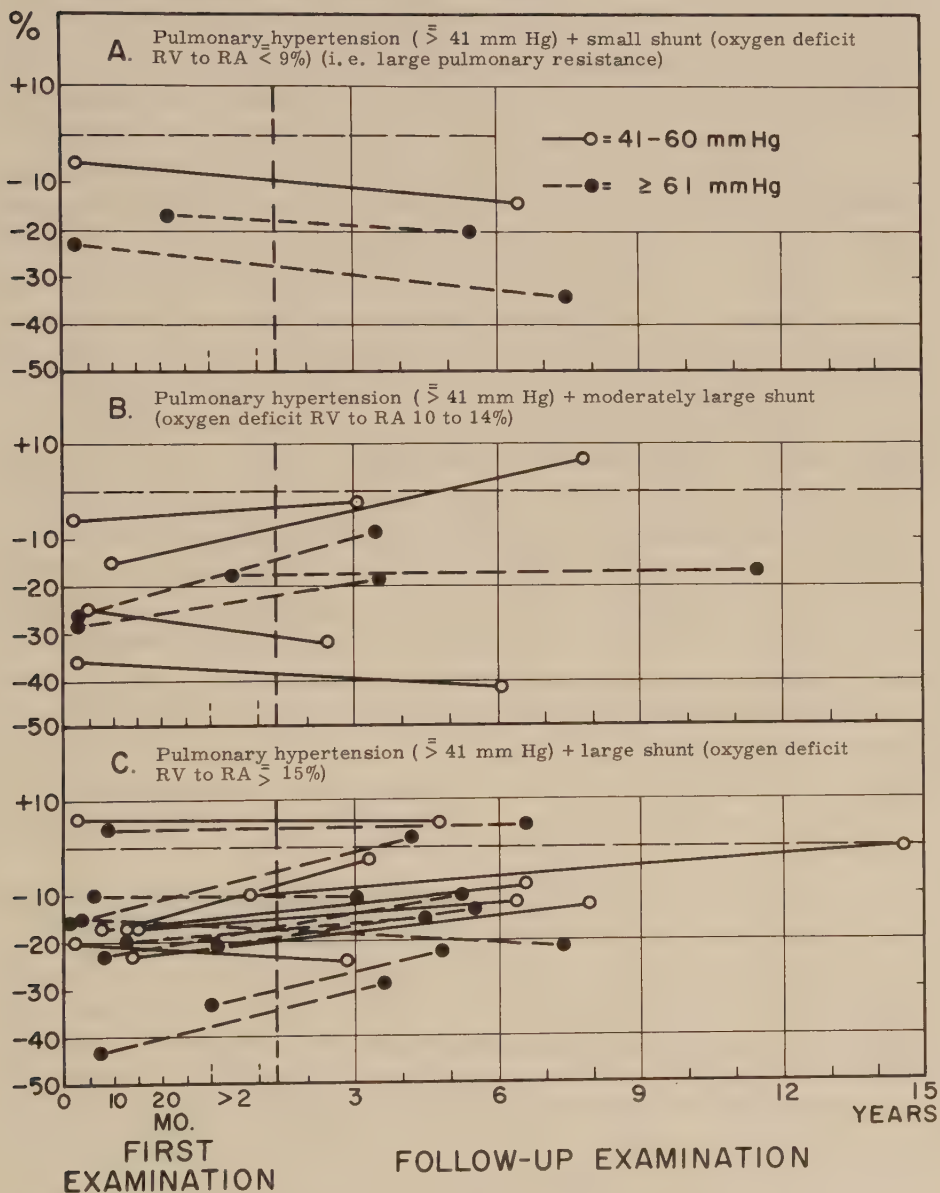
Voussure

Voussure is found at follow-up examination in 13 out of the 15 patients operated on. Furthermore, voussure is found in 33 out of the 60 patients not operated on, by comparison with 43 out of the 124 patients at first cardiological examination, so that the frequency of voussure has been increasing with increasing age. Also as at the first cardiological examination (see page 43), voussure is seen to increase with increasing pressure in the RV or PA, but on the other hand it is not seen to increase with certainty with increasing size of left-to-right shunt. Voussure was most often absent in the small hearts, and most rarely absent in very large hearts. In the patients who underwent palliative operation, voussure was found most frequently in the enlarged hearts.

Thrill

All but 2 of those who underwent palliative operation had thrill. In the patients who were not operated on, thrill was found on follow-up examination in 42 out of 60 (with fairly uniform distribution among the various groups of pressure value and shunt size), but only in 32 out of 124 at first cardiological examination. The frequency of thrill also increases with increasing age. Those patients who were not operated on, and who did not have thrill at follow-up examination (18), were also more or less uniformly distributed among the various pressure and shunt groups. Among those who underwent palliative operation, thrill occurred in all those 13 in whom the murmur was reported as "moderately strong" or stronger. In the case of the 2 patients who did not have thrill, the strength of the murmur was found to be "moderately strong" (1) and "strong" (1). As reported, thrill was recorded in 42 of those patients not operated on. In 95% of them, it was found together with moderately strong or stronger murmur, and only in 5% together with weak murmur. Those patients not operated on who did not present thrill at follow-up examination (18), were distributed more uniformly over the various degrees of strength of systolic murmur.

Fig. 14. Weight in relation to weight-for-age, at first cardiological examination and at follow-up examination, in 26 children with VSD who did not undergo surgical treatment (22 of whom were under 2 years of age at first cardiological examination). All had pulmonary hypertension at first cardiological examination, and all had cardiac disease as sole cause of failure to thrive. The patients are grouped in three groups according to size of shunt (left-to-right).



Murmur

At follow-up examination, those patients who were operated on all had a murmur which was "moderately strong" or stronger. In the patients who were not operated on, the majority had a "strong" murmur at follow-up examination: in 53 it was moderately strong or stronger. Comparing these follow-up results in the patients not operated on with the results from their first cardiological examination, the distribution is seen to have more or less the same pattern, although at first cardiological examination 97% of the murmurs were at most "moderately strong" or stronger, but only 88% had this classification at the follow-up examination. This may be due to the fact that the wall of the thorax is thinner in infants than in older children. Of the 6 patients who were not operated on and who had a weak murmur at follow-up examination, 3 had a systolic pressure at first examination of 20 mm Hg (no. 224), 33 mm Hg (no. 408) and 28 mm Hg (no. 476), i. e. no pulmonary hypertension; 2 of the 6 patients had severe pulmonary hypertension at first examination: a systolic pressure in RV or PA = 86 mm Hg (no. 277) and 79 mm Hg (no. 334); the last patient of the 6 (no. 550), who had a systolic pressure in RV or PA at first cardiological examination = 41 mm Hg, was found at recatheterization when almost 3 years of age to have developed a systolic pressure in RV or PA of 100 mm Hg. The weak systolic murmur in the first 3 patients mentioned (nos. 224, 408 and 475) may be interpreted as a sign of a development towards spontaneous closure of the defect, while in the last 3 patients (nos. 277, 334 and 550) the weak murmur at the follow-up examination has presumably been due to equalization between the ventricles, resulting in a strong reduction in the flow through the defect.

Neurological and mental disturbances

Finally, those neurological and mental disturbances will be reviewed which were demonstrated in the patients at the follow-up examination. Two mongols, 2 oligophrenics (one of them with epilepsy) and one case of slight tetraplegia had already been recognized at the first examination. Only one further case, of slight mental retardation, had appeared on follow-up examination, and no causal relationship is considered to exist between cardiological and mental or neurological disease in the 8% of the patients where the possibility of this is present, apart from the well-known tendency to congenital heart disease among mongols.

Concluding remarks

It may be said that with regard to the clinical results of the follow-up examination, the anamnesic symptoms (failure to thrive, shortness of breath, tendency to cyanosis at rest, and recurrent pulmonary infections) have decreased considerably from the first examination to the follow-up examination, both in those operated on and in those not operated on, both in pulmonary hypertension and in its absence, and in the case of both large and small left-to-right shunts, while reduced endurance has become more pronounced. However, those operated on have a greater tendency to cyanosis on effort than those not operated on, because of the artificial pulmonary stenosis. Tachypnoea on effort followed in incidence by reduced endurance are the most frequent complaints, as also observed by Sandøe (1963).

The sole clinical and physical finding which had decreased with certainty was tachypnoea. The frequency of voussure and thrill had increased. The weight, and in particular the weight-for-age, shows a pronounced dependence on the pressure in RV or PA measured at first examination. The lower the pressure, the greater the number of patients who developed a normal weight up to the time of the follow-up examination, and conversely. The same tendency held in the case of those who underwent palliative operation. These findings correspond to those reported by Morrow and Braunwald (1961), Craig and Sirak (1963), Verney et al. (1964), Goldblatt et al. (1965 a, 1965 b) and Takahashi et al. (1968). Albert et al. (1961) and Willman et al. (1962), on the other hand found a normal post-operative weight. The change in weight showed an even clearer dependence on the pulmonary hypertension. A comparison between weight-for-height and weight-for-age in 2 hemodynamically comparable groups of patients operated on and not operated on showed no definite difference; however, the group of patients operated on had been originally in a poorer clinical condition than those not operated on.

In those patients with pulmonary hypertension who were not operated on, grouping according to the presumed size of the pulmonary vascular resistance shows that it is the patients with the high pulmonary vascular resistance who continue to thrive poorly. Height at follow-up examination tends to become normalized in relation to height at first examination. Five patients, none of them operated on (one of them more than 2 years of age at first examination) showed clinical signs of cyanosis at rest at follow-up examination; they all had a very high systolic pressure in RV or PA at first examination, and presumably have developed into patients with Eisenmenger's syndrome or Fallot's tetralogy.

Voussure and thrill are recorded considerably more frequently at follow-up examination than at first cardiological examination.

The distribution of the maximum of the systolic murmur in the follow-up examination is more or less the same as at the first examination.

Radiological picture on follow-up examination

Introduction

The radiological examinations on which the follow-up examination is based were made using the same recording technique as employed at the first cardiological examination. Those patients who attended the follow-up examination as out-patients, however, only had a radiological examination of the thorax in the sagittal and frontal plane. The results of the radiological findings at the follow-up examination have been recorded for convenience in the same table as those for the first cardiological examination (table 19, page 52). At the follow-up examination, a determination of the volume of the heart was possible in only 74 children. Only 64 of the 75 who were followed-up had undergone a radiological examination of the thorax in 2 planes at the first examination, thus permitting a comparative volume determination of the heart. The relative volume of the heart was reviewed with regard to development during the period from the first examination to the follow-up examination, grouped into various pressure groups (from the first examination) and into patients not operated on contra patients who underwent palliative operation.

In the pressure group 0-40 mm Hg (both those under and over the age of 2 years at first examination), it was found that the relative heart volume had been maintained rather constant or had fallen slightly from the first examination to the follow-up examination. Only one patient without pulmonary hypertension deviated to a pronounced degree from the rest of the patient group, namely no. 272, in whom the relative heart volume increased from 385 ml at first examination aged 7 months to 760 ml at follow-up examination aged 4 years and 10 months. Clinically (anamnesic and physical findings) and radiologically (strongly increasing relative heart volume, prominence of the pulmonary conus at follow-up examination, while normal at first examination, and increasing pulmonary vascular density from first examination to follow-up examination), but hardly electrocardiographically (first examination: LAD, LVH, follow-up examination: normal axis, CVH), this patient deviates so much from the usual course in patients with the pressure findings and the left-to-right shunt values found at first examination (systolic pressure in RV or PA of 27 mm Hg, left-to-right shunt expressed as oxygen saturation deficit

from RV to RA of 8%), that it has not been possible to avoid reevaluating the diagnosis "isolated VSD", and the following diseases have been considered: 1) a complicated ASD; against this is the observation of normal pressure in RA, and that the difference in oxygen saturation between the mean value in the venae cavae (84%) and the RA (78%) is not significant. 2) An AVC instead of an isolated VSD; against this is again the normal pressure in RA, and in addition the low oxygen saturation percentage (78%) in RA. 3) an abnormal development in the pulmonary vessels with an abnormally strong dilatation of the entire pulmonary vascular tree, particularly the small vessels, but against this are the ECG changes on the one hand, and on the other hand the fact that the low pressure and shunt values in this patient can hardly be expected to have resulted in pulmonary vascular changes so severe primarily as to be unable to decrease with such abnormal rapidity and strength later. 4) a disease of the walls of the left chambers (LA and LV), but this would result in a different ECG, even though the other findings were compatible with this. It was therefore necessary to recognize that a satisfactory explanation could not be given for the strong clinical and roentgenological changes in the patient's condition. In this group of pressure values from 0-40 mm Hg there was one case of spontaneous closure of the VSD.

In the pressure group 41-60 mm Hg, the relative volume likewise remained more or less constant or fell slightly from the first examination to follow-up examination in the patients who were not operated on. From first examination to follow-up examination, one patient had developed severe pulmonary hypertension (a pressure rise in RV or PA from 41 to 100 mm Hg), with almost disappearance of the original large left-to-right shunt, i. e. this patient presumably had a strongly progressive disease of the pulmonary arterioles as an explanation for the increase in his relative heart volume. However, the patient was still acyanotic at follow-up examination. In this group, the only patient who was over 2 years of age at first examination increased in relative heart volume from first examination to follow-up examination 4 1/2 years later; this increase in relative heart volume was primarily due to a rise in the pulmonary pressure.

In the pressure group ≥ 61 mm Hg in RV or PA at first examination, the general tendency in the development of the relative heart volume was that in the case of the patients not operated on, it remained more or less constant or fell slightly. However, it rose in 3 patients, presumably due to the fact that all 3 had a very severe pulmonary hypertension already at first examination. In this pressure group, one patient differs completely from the others, as having a very high relative volume at first examination at the age of 2 months, and on recatheterization at the age of 16 months. On follow-up examination,

Table 35. Size of left atrium, evaluated from a radiological examination of the thorax at follow-up, in 74 out of 75 children with isolated VSD (one could not be evaluated), in relation to the pressure in RV or PA in mm Hg, and to the left-to-right shunt expressed by the oxygen saturation deficit from RV to RA in %, at first cardiological examination. The figures in brackets give the corresponding numbers from the radiological examination at first cardiological examination, in the case of 68 of the same 75 children (7 cases could not be evaluated).

Pressure in RV or PA	Size of left atrium						total
	normal		sl. enlarged		enlarged		
	op. on	not op. on	op. on	not op. on	op. on	not op. on	
0-40	0(0)	27(25)	0(0)	1(1)	0 (0)	0 (2)	28(28)
41-60	1(0)	11 (6)	0(0)	1(0)	3 (4)	2 (7)	18(17)
≥ 61	10(1)	10 (4)	0(0)	1(0)	1 (7)	6(11)	28(23)
total	11(1)	48(35)	0(0)	3(1)	4(11)	8(20)	74(68)
Oxygen deficit RV to RA							
0-9	2(0)	16(12)	0(0)	1(1)	0 (1)	0 (3)	19(17)
10-19	6(1)	18(17)	0(0)	1(0)	2 (6)	6 (9)	33(33)
≥ 20	3(0)	14 (4)	0(0)	1(0)	2 (4)	2(10)	22(18)
total	11(1)	48(33)	0(0)	3(1)	4(11)	8(22)	74(68)

Table 36. Size of left ventricle, evaluated from a radiological examination of the thorax at follow-up, in 75 children with isolated VSD, in relation to the pressure in RV or PA in mm Hg, and to the left-to-right shunt expressed by the oxygen saturation deficit from RV to RA in %, at first cardiological examination. The figures in brackets give the corresponding numbers from the radiological examination at first cardiological examination, in the case of the same 75 children.

Size of left ventricle							
Pressure in RV or PA	normal		sl. enlarged		enlarged		total
	op. on	not op. on	op. on	not op. on	op. on	not op. on	
0-40	0 (0)	16(14)	0 (0)	6 (5)	0 (0)	7(10)	29(29)
41-60	1 (0)	2 (2)	1 (0)	6 (5)	2 (4)	6 (7)	18(18)
≥ 61	6 (2)	1 (2)	1 (2)	1 (0)	4 (7)	15(15)	28(28)
total	7 (2)	19(18)	2 (2)	13(10)	6(11)	28(32)	75(75)

Oxygen deficit RV to RA							
0-9	2 (0)	10 (9)	0 (1)	2 (4)	0 (1)	5 (4)	19(19)
10-19	4 (2)	6 (6)	0 (1)	6 (3)	4 (5)	14(17)	34(34)
≥ 20	1 (0)	4 (3)	2 (0)	5 (3)	2 (5)	8(11)	22(22)
total	7 (2)	20(18)	2 (2)	13(10)	6(11)	27(32)	75(75)

Table 37. Density of pulmonary vasculature evaluated from a radiological examination of the thorax at follow-up in 75 children with isolated VSD, in relation to the pressure in RV or PA in mm Hg and to the left-to-right shunt at first cardiological examination, as well as to the heart volume/m² body surface at follow-up (only 74 of the 75 were included in this last determination, as one estimate of heart volume could not be made at follow-up due to lack of a lateral film). The figures in brackets give corresponding numbers from the radiological examination at first cardiological examination. The heart volume determination at the first radiological evaluation of this includes only 64 of the 75 children, as a lateral film was lacking in 11 cases.

Density of pulmonary vasculature									
Pressure in RV or PA	normal		sl. increased		increased		much increased		total
	op. on	not op. on	op. on	not op. on	op. on	not op. on	op. on	not op. on	
<40	0(0)	11(12)	0(0)	9 (6)	0 (0)	9 (9)	0(0)	0 (2)	29(27)
41-60	2(0)	2 (3)	0(0)	8 (1)	2 (3)	3 (6)	0(1)	1 (4)	18(18)
≥ 61	2(0)	0 (0)	5(1)	1 (5)	4 (7)	12 (8)	0(3)	4 (4)	28(28)
total	4(0)	13(15)	5(1)	18(12)	6(10)	24(23)	0(4)	5(10)	75(75)
Oxygen deficit V to RA									
<9	0(0)	7(11)	2(0)	5 (2)	0 (1)	4 (4)	0(1)	1 (0)	19(19)
10-19	2(0)	4 (2)	2(0)	5 (6)	4 (5)	16(12)	0(3)	1 (6)	34(34)
≥ 20	2(0)	2 (2)	1(1)	8 (3)	2 (4)	4 (8)	0(0)	3 (4)	22(22)
total	4(0)	13(15)	5(1)	18(11)	6(10)	24(24)	0(4)	5(10)	75(75)
Heart volume m ² body surface									
< 299	0(0)	1 (5)	0(0)	0 (0)	0(0)	1 (2)	0(0)	0(0)	2 (7)
300-399	0(0)	10 (6)	1(0)	3 (5)	1(0)	4 (6)	0(0)	0(0)	19(17)
400-499	1(0)	2 (5)	4(0)	9 (4)	1(3)	8 (6)	0(0)	0(3)	25(21)
≥ 500	3(0)	0 (0)	1(0)	6 (2)	3(6)	10 (5)	0(3)	5(3)	28(15)
total	4(0)	13(16)	6(0)	18(11)	5(9)	24(19)	0(3)	5(6)	74(64)

Table 38. Appearance of the pulmonary conus on radiological examination of the thorax at follow-up examination in 75 children with isolated VSD, in relation to the pressure in RV or PA in mm Hg and to the left-to-right shunt expressed by the oxygen saturation deficit from RV to RA in %, at first cardiological examination. 15 out of the 75 children underwent palliative operation after the first examination, all under the age of 2 years. The figures in brackets give the corresponding numbers for the same children at the first examination (with the exception of 5 for whom information on the pulmonary conus is not available).

Pulmonary conus					
Pressure in RV/PA	concave	normal	normal contour disappeared	prominent	total
all operated on	2 (0)	3 (3)	7 (3)	3 (7)	15 (13)
not operated on					
0-40	0 (0)	15 (18)	4 (4)	10 (7)	29 (29)
41-60	0 (0)	8 (6)	4 (3)	2 (4)	14 (13)
≥ 61	0 (0)	8 (7)	1 (3)	8 (5)	17 (15)
total	2 (0)	34 (34)	16 (13)	23 (23)	75 (70)

Oxygen deficit RV to RA					
all operated on	2 (0)	3 (3)	7 (3)	3 (7)	15 (13)
not operated on					
0-9	0 (0)	10 (12)	3 (2)	4 (2)	17 (16)
10-19	0 (0)	11 (12)	5 (4)	10 (8)	26 (24)
≥ 20	0 (0)	10 (7)	1 (4)	6 (6)	17 (17)
total	0 (0)	34 (34)	16 (13)	23 (23)	75 (70)

the relative volume had fallen to below the first two measurements. This patient had presumably developed a large relative heart volume as the result of severe progressive vascular changes in the lungs, terminating in a slow fall in the relative heart volume (together with cyanosis) as a sign that the condition had reached a stage corresponding to Eisenmenger's syndrome. The patients from pressure groups 41-60 mm Hg and ≥ 61 mm Hg (at first examination) who underwent palliative operation all showed a decreasing relative heart volume. None of the patients who had undergone palliative operation had increased in relative heart volume from the first examination to the follow-up examination. If the patients who were not operated on, and who had pulmonary hypertension, are grouped according to the various shunt sizes (as found at first examination), this grouping shows no definite difference between the various shunt sizes with respect to influencing the development of the relative heart volume.

As a main rule, the size of the heart evaluated on the basis of the measurements of the relative volume of the heart in those infants who were not operated on, did not change very much from first examination to follow-up examination, either in patients under or in patients over the age of 2 years at first examination, although the relative heart volume has shown a certain tendency to fall slightly. In the case of patients who underwent palliative operation, there was a fall in the size of the heart from first examination (before operation) to follow-up examination. In the present material, the pressure gradient obtained in the palliative operation was found to have no correlation with the post-operative size of the heart.

The size of LA and of LV at follow-up examination (tables 35 and 36) is thus found to be well correlated with pressure and left-to-right shunt (at first examination), and the follow-up examination also showed a tendency to a normalization or a decrease in the size of the two chambers, when a comparison was made with the findings from the first examination (in the same patients); this tendency is greatest in LA. The change is most pronounced for patients with pulmonary hypertension (including those who underwent palliative operation). In the case of the left-to-right shunt, the above correlation holds for all magnitudes of shunt (including those patients who underwent palliative operation). In this connection, the density of pulmonary vascularization (table 37) in relation to pressure and left-to-right shunt is also found to have decreased from first examination to the follow-up examination; this is particularly pronounced in the case of the patients who underwent palliative operation. The same relationship holds when the density of pulmonary vascularization is related to the relative volume of the heart, and where the patients who were operated on also show the most pronounced increase in den-

sity of pulmonary vascularization. The findings presented here on changes in the size of LA and LV and the decrease in the density of pulmonary vascularization correspond closely to the reports in the literature (Campbell 1951, Keats et al. 1956, Nadas 1957, Loogen 1958, Bell et al. 1959, Blount and Woodwark 1960, Dammann et al. 1960, Edwards 1960, Weidman et al. 1963, Iverson et al. 1966, Dammann and Carpenter 1968). The pulmonary conus (table 38), on the other hand, has not changed particularly from first examination to follow-up examination, either in the patients not operated on or in the patients operated on, as also found by Capp et al. (1968) and Simon (1968), but those patients in the present material who are presumed to have developed an Eisenmenger's syndrome did not show any decreasing pulmonary markings peripherally, as has been described by Kjellberg et al. (1955), Hubbard et al. (1957), Weidman et al. (1963), Capp et al. (1968) and Simon (1968). Capp et al. (1968), however, draw attention to the fact that a recognition of the distinction between the narrow peripheral and the wide central pulmonary vessels may be extremely difficult in infants and small children. The unchanged size of the pulmonary conus may possibly be explained by an increasing resistance to the passage of the blood through the pulmonary arterioles in the patients not operated on and to a prestenotic dilatation of the pulmonary conus in those patients operated on.

Two of those patients operated on (by the Dammann-Muller method and the Dammann-Muller modificata), however, had a concavity corresponding to the pulmonary conus, possibly because the method of operation described results in a rather long stenosis which may conceivably become complicated with a proximal muscular hypertrophy, similar to the infundibular stenosis in Fallot's tetralogy.

At follow-up examination, 5 of the patients were cyanotic (nos. 29, 214, 277, 334 and 422) and were presumably approaching a stage corresponding to an Eisenmenger's syndrome, but this could not be seen from the density of the pulmonary vascularization (in particular, it was not possible to demonstrate the characteristic difference described in the literature between the wide central pulmonary vessels and the narrow peripheral pulmonary vessels). The density of the pulmonary vascularization was either unchanged from the first examination (in 3) or had even increased (in 2). It is possible that a few years' longer observation period would have given the characteristic picture. Furthermore, one patient had developed an infundibular stenosis (no. 23) from the first examination to the follow-up examination, but neither in this patient was it possible to see any reduction in the density of the pulmonary vascularization, which if anything had increased. Finally, up to the time of the follow-up examination, one patient had developed a severe pulmonary hypertension from

a slight pulmonary hypertension at first examination (no. 550), and this patient - who was not cyanotic on follow-up examination - is the only patient who showed a decreasing density of pulmonary marking from the first examination to follow-up examination, as might be expected in the case of severe progressive narrowing of the pulmonary arterioles.

Electrocardiography at follow-up examination

Introduction

In the follow-up examination of the 75 children, 63 of them under the age of 2 years at first examination, an ECG was carried out in all (with the exception of one who was examined in Greenland). Just as in the case of the first examination, 3 standard limb leads were taken (I, II and III), 3 unipolar extremity leads (aVR, aVL and aVF) and 6 precordial leads (V_1 - V_6) (vector-cardiography was not carried out), and the norms are the same as in the first examination, but taking into account the change in age.

A review of the ECG findings at follow-up examination shows that within those constellations which are either normal or which include some signs of affection of the left side of the heart (without or with involvement of the right side of the heart), there is a tendency towards a change from the first examination to the follow-up examination in the direction of improvement in those ECG constellations which are abnormal, while in the ECG constellations which mainly or exclusively show right axis deviation, a tendency is seen for the development from the first examination to the follow-up examination to be either slight (RAD+CVH), or in the most abnormal group (RAD+RVH), increasing in the direction of a grave prognosis. The observed changes are fairly uniformly distributed over the various magnitudes of shunts and also over the various magnitudes of pressure in RV or PA (although in the case of the most abnormal ECG constellations, they undoubtedly accumulate in the high pressure groups). With regard to the relationship to the various sizes of heart volume, the ECG changes involve mainly the slightly enlarged hearts. In the case of the patients who were operated on, the changes have generally been in the direction of an increase in the ECG constellations with right axis deviation, as might be expected, since the palliative operation involves a reduction in the outflow from the RV, and in consequence an overload on the RV.

The electric axis

The grading normal axis $\rightarrow$ LAD $\rightarrow$ RAD may be used more or less corresponding to good $\rightarrow$ poor prognostic development. In the case of the patients shown in table 39 (all grouped according to the magnitude of the systolic pressure in RV or PA at first examination, which as previously mentioned shows the best correlation with the degree of severity of the disease), this will mean that in the children not operated on (under the age of 2 years at first examination), 19 out of the 21 in the pressure group $\bar{<}$ 40 mm Hg improved or remained unchanged; only 2 deteriorated (and only from normal axis to LAD). In the pressure group 41-60 mm Hg, 11 out of the 13 improved or remained unchanged, while 2 deteriorated (here, the normal axis was changed to RAD, and in one case an excessive RAD); in the pressure group $\bar{>}$ 61 mm Hg, 10 out of 14 improved or remained unchanged, while 4 deteriorated. The tendency to a stabilization or an improvement in the electric axis is clear in all the pressure groups.

In the case of the 15 patients who underwent palliative operation (table 40), a tendency is seen to right axis deviation. It should be mentioned here that the case of LAD marked with x should most probably have had a direction more than -90° (between -90° and $+180^\circ$), in other words have been an excessive RAD judging by the course (this also holds for the case of LAD marked in the same manner in table 41), as was also to be expected on recalling that in the patient in table 40, the flow in the PA has been restricted, with consequent overload on RV. In the patient in table 39, a development from LAD to excessive RAD is unlikely with the high pressure in RV or PA. While only 8 out of the 15 children had RAD preoperatively, this was the case in 12 (possibly 11) post-operatively. Table 40 also shows the time which has elapsed from operation to follow-up examination, for the various axis deviations, on the assumption that the longer this period of time, the greater the tendency to right axis deviation, but this is only found in the group which commenced with a normal axis; presumably, however, in a number of cases the period of observation had been too brief to allow this tendency to a right axis deviation to appear completely.

In those children who were over the age of 2 years at first examination, none of them operated on (table 41), there appears to be a pronounced tendency to stability of the electric axis from the first examination to the follow-up examination.

Table 39. Changes in the electric axis on the ECG from the first examination to the follow-up examination in 48 children with isolated VSD who were not operated on, and who were under the age of 2 years at first examination, grouped according to the pressure in the RV or PA at first examination.

	First examination	Follow-up examination
21 children with pressure in RV or PA ≤ 40 mm Hg	$\left\{ \begin{array}{l} 15 \text{ normal axis} \\ 4 \text{ LAD} \\ 2 \text{ RAD} \end{array} \right.$	$\left\{ \begin{array}{l} 13 \text{ normal axis} \\ 2 \text{ LAD} \\ 1 \text{ normal axis} \\ 3 \text{ LAD} \end{array} \right.$ 2 normal axis
13 children with pressure in RV or PA = 41 - 60 mm Hg	$\left\{ \begin{array}{l} 8 \text{ normal axis} \\ 2 \text{ LAD} \\ 3 \text{ RAD} \end{array} \right.$	$\left\{ \begin{array}{l} 6 \text{ normal axis} \\ 2 \text{ RAD (1 excessive)} \\ 2 \text{ LAD} \\ 1 \text{ normal axis} \\ 2 \text{ RAD} \end{array} \right.$
14 children with pressure in RV or PA ≥ 61 mm Hg	$\left\{ \begin{array}{l} 6 \text{ normal axis} \\ 4 \text{ LAD} \\ 4 \text{ RAD (2 excessive)} \end{array} \right.$	$\left\{ \begin{array}{l} 3 \text{ normal axis} \\ 1 \text{ LAD} \\ 2 \text{ RAD} \\ 1 \text{ normal axis} \\ 2 \text{ LAD} \\ 1 \text{ RAD (excessive)} \\ 1 \text{ LAD}^{\text{x)}} \\ 3 \text{ RAD (1 excessive)} \end{array} \right.$

x) Should presumably have been excessive RAD, see text

Table 40. Changes in the electric axis on the ECG from the first examination to the follow-up examination, in 15 children with isolated VSD who were operated on following first examination under the age of 2 years, all of whom had pulmonary hypertension at first examination.

	First examination	Follow-up examination	No. of years from operation to follow-up exam. (mean)
15 children under the age of two years at first exam., all operated on	4 normal axis	{ 2 normal axis 2 RAD (1 excessive)	3 10/12 5 5/12
	3 LAD	{ 1 LAD 2 RAD (1 excessive)	3 5/12 2 9/12
	8 RAD (4 excessive)	{ 1 LAD ^{x)} 7 RAD (3 excessive)	4 1/12 3 7/12

x) Should presumably have been excessive RAD, see text

Table 41. Changes in the electric axis on the ECG from the first examination to the follow-up examination, in 12 children with isolated VSD who were over the age of 2 years at first examination, grouped according to pressure in RV or PA at first examination.

	First examination	Follow-up examination
12 children over 2 years of age, none operated on	8 with pressure in RV or PA ≤ 40 mm Hg	{ 6 normal axis 2 LAD
	1 with pressure in RV or PA = 41-60 mm Hg	1 normal axis
	3 with pressure in RV or PA ≥ 61 mm Hg	{ 1 LAD 2 RAD

Table 42. Changes in ventricular hypertrophy on the ECG from the first examination to the follow-up examination in 44 out of 48 children with isolated VSD, all under the age of 2 years at first examination, none of them operated on (3 had no precordial leads at first examination, one had no precordial leads at follow-up examination), grouped according to pressure in RV or PA at first examination.

	First examination	Follow-up examination
19 children with pressure in RV or PA ≤ 40 mm Hg	11 no ventricular hypertrophy 1 LVH 7 CVH	8 no ventricular hypertrophy 3 LVH 1 CVH 3 no ventricular hypertrophy 2 LVH 2 CVH
12 children with pressure in RV or PA = 41-60 mm Hg	3 no ventricular hypertrophy 1 LVH 7 CVH 1 RVH	1 no ventricular hypertrophy 1 LVH 1 RVH 4 no ventricular hypertrophy 1 LVH 2 CVH 1 RVH
13 children with pressure in RV or PA ≥ 61 mm Hg	2 no ventricular hypertrophy 1 LVH 8 CVH 2 RVH	2 no ventricular hypertrophy 1 RVH 2 LVH 4 CVH 2 RVH 1 LVH 1 RVH

Table 43. Changes in ventricular hypertrophy on the ECG from the first examination to the follow-up examination in 15 children with isolated VSD who were under the age of 2 years at first examination, all with pulmonary hypertension and all operated on after the first examination.

	First examination	Follow-up examination	Age from operation to follow-up exam. in years (mean)
15 children under 2 years of age at first exam., all operated on	14 CVH	2 no ventricular hypertrophy	2 9/12
		1 LVH	6 11/12
		6 CVH	3 3/12
		5 RVH	4 10/12
	1 RVH	no ventricular hypertrophy	1 11/12

Table 44. Changes in ventricular hypertrophy on the ECG from the first examination to the follow-up examination in 12 children with isolated VSD who were all over the age of 2 years at first examination, none of them operated on, grouped according to pressure in RV or PA at first examination.

	First examination	Follow-up examination
12 children over the age of 2 years at first exam.	8 with pressure in RV or PA $\bar{<}$ 40 mm Hg	5 no ventricular hypertrophy
		2 LVH
		1 CVH
	1 with pressure in RV og PA = 41-60 mm Hg	1 LVH
	3 with pressure in RV or PA $\geq$ 61 mm Hg	1 no ventricular hypertrophy 1 CVH 1 RVH

Ventricular hypertrophy

In a corresponding manner, using a grading: no ventricular hypertrophy $\rightarrow$ LVH $\rightarrow$ CVH $\rightarrow$ RVH as an expression for a good $\rightarrow$ poor prognostic development, the same considerations can be presented for the development of ventricular hypertrophy from first examination to follow-up examination.

Table 42 shows the development of ventricular hypertrophy from first examination to follow-up examination in 44 children under the age of 2 years at first examination, none of them operated on, grouped according to the systolic pressure in RV or PA at first examination: in pressure group ≤ 40 mm Hg, 15 of the 19 children improved or remained unchanged from first examination to follow-up examination, while 4 deteriorated (although none of them developed RVH). In the pressure group 41-60 mm Hg, 10 of the 12 improved or remained unchanged from first examination to follow-up examination, while 2 deteriorated (one of whom developed RVH). In the pressure group ≥ 61 mm Hg, 10 of the 13 improved or remained unchanged, while 3 deteriorated (all 3 having developed RVH).

Table 43 shows the changes in ventricular hypertrophy from first examination to follow-up examination in the 15 children who were operated on. It is seen that in 14 of them, who had CVH at first examination, their condition had improved or remained unchanged in 9, while only 5 showed a development towards a condition of RVH. Further, the only patient who had RVH before the operation, developed favourably to a stage where no ventricular hypertrophy could be found at follow-up examination. While one of the 15 children had RVH at first examination, 5 of them had RVH at follow-up examination (after the palliative operation had been carried out shortly after the first examination). The period from the operation to the follow-up examination is shown for the various types of ventricular hypertrophy at follow-up examination, but neither here (cf. the condition with regard to the electric axis) is any definite correlation found between the period elapsing from operation to follow-up examination, and the tendency to the development of RVH. As previously mentioned, it must be assumed that part of the explanation for this is that the period of observation has been too short in some of the patients.

Table 44 shows the development of ventricular hypertrophy from first examination to follow-up examination in the 12 children who were over the age of 2 years at first examination, none of them operated on, grouped according to the 3 types of pressure grouping already employed. The general tendency in development is a stability in the ventricular hypertrophy from first examination to follow-up examination; only one patient - in the group with pressure $\geq$

61 mm Hg - developed from CVH to pure RVH, which must be regarded as a deterioration from a prognostic point of view.

In table 45, those 5 patients have been selected from the previous tables (of patients not operated on) who may be presumed to have developed an Eisenmenger's syndrome, together with the one patient in whom the low pulmonary hypertension at first examination had developed at follow-up examination into a very severe pulmonary hypertension (although without cyanosis), with the aim of determining how this special group of patients in particular had fared. All the first 5 patients mentioned had developed right axis deviation, together with a right ventricular hypertrophy with the exception of 2, who already had the constellation RAD+CVH; these remained unchanged (and perhaps might have a chance of a favourable result from a corrective operation). The last-mentioned single patient, who developed very severe pulmonary hypertension from first examination to follow-up examination, had on follow-up RAD+RVH, as was to be expected (patient no. 23, who developed an infundibular stenosis from first examination to follow-up examination, had on the latter occasion LAD+CVH, the explanation for which might be that the increasing obstruction in the outflow region from the RV had made it possible for the thickness of the media in the pulmonary arterioles to decrease, with the result of falling resistance in the pulmonary vascular tree and increased blood flow through this. Support for this explanation is found in the observation that the pulmonary vascular density increased from first examination to the follow-up examination (see page 112). (The patient with the spontaneous closure of VSD had no axis deviation or ventricular hypertrophy either at first examination or at follow-up examination, and this result at follow-up examination corresponds to what would have been expected).

Block

With the criteria for incomplete and complete branch block which have been employed at first cardiological examination, no case was found of incomplete or complete branch block at follow-up examination; the one patient who had incomplete right branch block at first examination is not included in the follow-up examination.

To conclude as to the development of the ECG from first examination to follow-up examination, it may be said in general that in the case of patients who were not operated on under the age of 2 years at first examination, a development takes place from the first examination to the follow-up examination, so that the least severe ECG constellations, in which the electric axis =

Table 45. Changes in electric axis + ventricular hypertrophy on the ECG in 6 children (5 under 2 years of age at first examination), from first examination to follow-up examination. All the children had pulmonary hypertension, severe in five (No. 29, 214, 277, 334 and 422). These 5 children were cyanotic up to the follow-up examination. One child (No. 550) had slight pulmonary hypertension at first examination, but developed severe pulmonary hypertension up to the follow-up examination (41 mm Hg to 100 mm Hg), although there were no cyanosis at the follow-up examination (these 6 patients are included in the preceding tables).

	First examination	Follow-up examination	
6	5 with severe pulmonary hypertension	1 normal axis, CVH	all cyanotic
		1 RAD, RVH	
		1 RAD, RVH	
	1 with slight pulmonary hypertension	3 RAD, CVH	no cyanosis but severe pulmonary hypertension
		2 RAD, CVH	
		1 RAD, RVH	
	1 normal axis, no ventricular hypertrophy	RAD, RVH	

P. S. Patient No. 23, who should have been included in this list, as a muscular obstruction developed in the outflow region (a PS), has not been included, as precordial leads were lacking at first examination. This patient had LAD and CVH at follow-up examination.

The patient with spontaneous closure of the VSD (No. 430) had no axis deviation or ventricular hypertrophy at first examination or follow-up examination.

normal axis or LAD, and where there is either no ventricular hypertrophy, LVH or CVH, tend towards an improvement, or possibly a normalization of the electric axis + ventricular hypertrophy. On the other hand, the severe ECG constellations: RAD+CVH and RAD+RVH, appear in general to become exacerbated from first examination to follow-up examination. In the case of children who have developed in the direction of an Eisenmenger's complex, the ECG usually appears to tend towards right axis deviation. In the case of children not operated on, examined for the first time after the age of 2 years, there is a considerable stability in the appearance of the ECG from the first examination to the follow-up examination. This corresponds to earlier reports (Selzer and Laqueur 1951, Braunwald et al. 1955, Brown et al. 1955, Nadas 1957, Keith et al. 1958, Loogen 1958, P. Wood 1958 a, Blount and Woodward 1960, Dack 1960, Edwards 1960, Scott 1961, Dammann and Carpenter 1968).

In the case of children who underwent palliative operation, the present material has shown a pronounced tendency to right axis deviation of the ECG from before the operation to the follow-up examination, which was from about 2 years after to more than 7 years after the operation, quite as reported by Gammelgaard et al. (1961), Bühlmeier et al. (1965), Goldblatt et al. (1965 a), Gerard et al. (1966) and Takahashi et al. (1968). No authors appear to have put forward any contrary views or findings.

Chapter XIV

Conclusions of the study, in particular on the aims of the investigation

The aims of the present study have been described on pages 11 and 12.

1. A thorough and detailed review has been provided of the disease picture "isolated ventricular septal defect" in children, based on a material of 144 children, 124 of whom were examined before the age of 2 years (103 before the age of 12 months, 71 before the age of 6 months). All the patients in the material underwent cardiac catheterization, and in a number of the patients there was further confirmation of the diagnosis on right-sided angiocardiology - most often selective - on operation and/or on autopsy. The disease picture in the children was elucidated both by the details of the anamnesis and clinically by physical examination, by radiological examination of the thorax and by electrocardiography. Because of its great preponderance of quite small infants, the material has made it possible to elucidate the disease picture right from the start of the disease, for all degrees of severity of the disease from the mildest to the most severe form, and, as a result of a follow-up examination, to examine the development of the disease from its first symptom until it led either to spontaneous improvement (possibly cure), to a more or less slow development of the final stage (corresponding to Eisenmenger's syndrome), or to death in acute cardiac failure, or - where palliative operative treatment was employed - to post-operative improvement, followed years later by a new exacerbation, indicating the need for corrective operative treatment.

2. It was shown that the use of anamnestic information, with clinical, radiological and electrocardiographic investigations and the support of electronic data processing of all this information, was not enough to make any statement, even with moderate certainty, as to the hemodynamic circumstances in any one patient. This meant that cardiac catheterization

(possibly supplemented by right-sided angiocardiography) was a necessary supplementary investigation to establish the hemodynamics of the heart disease and thereby to provide a prognosis for each separate patient, including a statement as to whether palliative operation might be worth discussing as treatment, so as to bear the patient over the most dangerous period in the early stages of the disease, the first six months of life of the infant. Where the hemodynamic conditions are known, it has been shown that among the most severe cases, there are 4 states in particular which tell for the necessity of a palliative operation, even though effective medical treatment has been instituted; 1. the occurrence of the following 6 clinical symptoms: tachypnoea at rest, tachypnoea on effort, cyanosis at rest, cyanosis on effort, failure to thrive on admission to hospital and hepatomegaly. Depending on how many of the six symptoms there are demonstrated, the more the weight which can be attached to point 1). 2. Failure to thrive in the hospital in spite of the optimal conditions being present to enable the child to thrive normally. 3. Cardiomegaly, expressed by the size of the relative volume of the heart when measured on a roentgenogram of the thorax. 4. Signs of left ventricular strain on the ECG.

In spite of the fact that a sufficiently satisfactory correlation has not been demonstrated between on the one hand clinical, radiological and electrocardiographic findings, and on the other hand the hemodynamic conditions, nevertheless with known catheterization findings it has been possible to confirm what had been accepted as a working hypothesis, namely, that the condition of the individual patient depends very much on the pressure in the right ventricle or pulmonary artery and on the magnitude of the left-to-right shunt between the ventricles, but particularly on the magnitude of the pressure, and that it has been of value to establish relationships between the individual symptoms in the patient and these two parameters.

3. Comparing the hemodynamically most severe cases which were treated conservatively and the equally severe hemodynamic cases (although clinically poorer) which were subjected to a palliative operation, the conclusion from the results of the follow-up examination is that at the follow-up examination, the patients operated on were placed clinically equal with the patients not operated on (and clinically improved), and that the palliative operation of surgical narrowing of the pulmonary artery has been beneficial for the patients both in the acute stage of their worst period (the first 6 months of life), as well as from a longer view. In the opinion of the author, the palliative operation continues to be justified, even bearing in mind the high operational mortality, provided the greatest care is taken in the selection of the patients for operation.

Summary

CHAPTER I

A brief account is given of the aims of the present study: 1. To review of the disease picture "isolated ventricular septal defect" (isolated VSD), as is observed in children in the age group mainly under the age of 2 years. 2. To examine the question whether cardiac catheterization and possibly right-sided angiocardiology can be dispensed with when there is a combination of sufficiently detailed anamnesis and clinical and physical findings, together with a radiogram of the thorax and an ECG. If the first-mentioned procedures cannot be dispensed with, then the question arises whether among the patients with the poorest condition it might be possible with the help of supplementary cardiac catheterization and if necessary right-sided angiocardiology, to distinguish a group requiring specially intense medical treatment, possibly a palliative operation. 3. To evaluate the results of the palliative operations.

CHAPTER II

The author's material consists of all those children who after cardiac catheterization at the Cardiological Laboratory of Queen Louise's Children's Hospital during the period August 1954 to the end of 1963 were diagnosed as having isolated VSD. Of 853 children with demonstrated heart disease, a total of 144 were found with isolated VSD, 124 of them under the age of 2 years at the time of the examination. Of the 97 children out of the 144 who were examined before the end of 1960, all but one of the 76 survivors underwent a follow-up examination before the end of 1963. The remaining 47

children from the period of investigation 1961-1963 did not undergo any follow-up examination. Information on those patients who were followed-up was brought up to date to the end of 1963 (with the exception of one patient). It is stressed that in the review of the material, emphasis has been on the children under the age of two years, the age period during which the greatest changes take place in children with isolated VSD. The incidence of isolated VSD among patients with congenital heart disease in the present material is found to be 16.9% of all children examined; 18.1% of the children examined who were under the age of 2 years. In a review of the etiology, the familial disposition in the present material is reported as 11.3%. Complications in the mother during pregnancy were found associated with 11.6% of the patients in the material. It is emphasized that only one case of infection (not specified) was reported during the first trimester of pregnancy, in other words no definite cases of rubella. The age of the parents does not deviate in this material from the age in the normal population, nor does the incidence of birth complications. On the other hand, the incidence of birth weight less than 2500 g is higher than in the normal population (17.7% compared to a value varying between 3% and 12% in the normal population). The distribution of the month of birth of the patients throughout the year shows no seasonal accumulation. Congenital non-cardiological defects (including mongolism) were found among 24.3% of the patients. The sex and age distribution of the material show 83 girls and 61 boys in a total material of 144 children (70 girls and 54 boys examined before the age of 2 years). There is no significant difference between the incidence of the two sexes. The tendency to a preponderance of girls is pointed out, as a preponderance of boys was to be expected. The youngest patients were under the age of 1 month, the oldest patient was 10 years old at first examination. Spontaneous mortality (i. e. not surgically determined) cannot be calculated in the material, as almost all the patients in the poorest condition have been referred for corrective or palliative operation. Only 6 patients died without having undergone operation.

CHAPTER III

Chapter III is a review of the anamnestic symptoms as well as the clinical and physical findings, in relation to the magnitude of the systolic pressure in RV or PA and to the magnitude of the left-to-right shunt expressed as the difference in oxygen saturation percentage between RV and RA (as the oxygen uptake through the lungs has not been measured in the patients in the mate-

rial, and the arterial oxygen saturation was measured in only very few. The magnitude of the systemic flow, the pulmonary vascular resistance and the flow ratio could therefore not be calculated). The literature on the clinical symptoms in isolated VSD was reviewed, followed by a review of the present material. The working hypothesis chosen has been that the condition of the patients depends in particular on the pressure in RV or PA and on the magnitude of the left-to-right shunt, so that the individual conditions reviewed have been evaluated in relation to these two parameters. The first cardiac symptom reported in the anamnesis was observed in 138 out of the 144 children before the age of 2 years, and in 120 out of the 144 children before the age of 6 months. It is demonstrated that the degree of severity, expressed by the magnitude of systolic pressure in RV or PA or by the size of the left-to-right shunt, does not influence the time at which the first anamnestic symptom is recognized. Those symptoms which lead earliest to a cardiological examination are failure to thrive and tachypnoea, whereas murmur as the sole symptom has not necessarily led to early cardiological examination. The reasons for referral for examination, such as recurrent pulmonary infections (with, as a result, the discovery of heart disease), inability to thrive and tachypnoea are often correlated with hemodynamically severe cases of isolated VSD, especially when evaluated on the basis of the magnitude of the pressure in RV or PA.

The 5 most important anamnestic symptoms, in order of frequency, are: inability to thrive, tachypnoea on effort, cyanosis on effort, tachypnoea at rest and recurrent pulmonary infections. A clear relationship has been found between the incidence of the symptoms and the magnitude of the systolic pressure in RV or PA, while this correlation has only been found to a slight degree in relation to the size of the shunt. It was also found that the greater the number of the most frequently occurring anamnestic symptoms in a patient, the more severe the disease when evaluated on the basis of the systolic pressure in RV and PA and - to a lesser degree - on the basis of the magnitude of the left-to-right shunt. In patients with pulmonary hypertension (systolic pressure in RV or PA ≥ 41 mmHg) or a shunt size - expressed by percentage oxygen saturation deficit RV-RA - $\geq 15\%$, 3 out of the 5 symptoms mentioned above are found in more than half of the patients.

The most frequently occurring clinical and physical finding is the systolic murmur (which occurred in 141 out of the 144 patients). The clinical and physical findings which occurred with the greatest frequency after this are, according to their incidence: inability to thrive, tachypnoea on effort, tachypnoea at rest, hepatomegaly and voussure. These 5 symptoms have shown an increasing incidence with increasing systolic pressure in RV or PA, but

this has been very much less pronounced with increasing size of shunt. The greater the number of these most frequently occurring clinical and physical findings (apart from murmur) in a patient, the more serious is the disease from a hemodynamic point of view. This is true both when the symptoms are related to the size of shunt and to the magnitude of the systolic pressure in RV or PA, but is most obvious in the latter case. In patients with a systolic pressure in RV or PA ≥ 61 mmHg, 4 out of 5 of the symptoms scheduled are found in almost $3/4$ of the patients, and with a shunt size $\geq 15\%$ (oxygen saturation deficit RV-RA), 4 out of the 5 symptoms mentioned are found in more than half of the patients.

The individual anamnestic symptoms and clinical and physical findings will now be described:

Inability to thrive as a symptom in the anamnesis is found with increasing frequency with increasing pressure in RV or PA, whereas the correlation with the size of the shunt is not striking. The observation that growth in length or growth in height is most often less inhibited than increase in weight, has been given a special designation, "poor growth" ("poor growth" occurs less frequently than failure to thrive). The dependence of weight-for-age - and to a lesser degree weight-for-height - on the systolic pressure in RV or PA is clearly seen; the greater the pressure the greater the inhibition in weight. On the other hand, inhibition of weight-for-age and weight-for-height does not appear to be definitely dependent on the size of shunt. If in patients with pressure equalization between the ventricles (in this study put at a systolic pressure in RV or PA ≥ 61 mmHg), it is permitted to assume that size of shunt is inversely proportional to the resistance in the pulmonary vessels, no definite correlation is found between the pulmonary vascular resistance and the magnitudes of the inhibition in weight (see however under follow-up examination, chapter XIII). The inhibition in growth-in-length or growth-in-height is found to be somewhat dependent on the magnitude of the pressure in RV or PA (although the influence is not strong), but it is only dependent to a slight degree on the size of the shunt. The inhibition in growth in the present material was not found to be dependent on the presence of recurrent infections of the pulmonary tract.

Tachypnoea at rest and on effort was found to increase with increasing pressure in RV or PA, but was not definitely dependent on the size of the shunt; in addition, the tachypnoea was found to be more frequent, the greater the relative volume of the heart.

Cyanosis at rest and on effort: it was not possible to distinguish between peripheral and central cyanosis in the anamnesis. Depending on the hemodynamic conditions, cyanosis may be caused by an intermittent right-to-left

shunt, especially cyanosis on effort. 16 patients under the age of 2 years had cyanosis on effort, and 15 of them had pulmonary hypertension with the possibility of pressure equalization between RV and LV. Another explanation for the cyanosis, however, could be a poor peripheral circulation. Finally, the possibility is present that the respiratory difficulties in cardiac failure may be the cause of the cyanosis, or may be contributory to it. Seven out of the 13 children with cyanosis on effort, for whom no information on the oxygen saturation in LA or LV was available, had signs of cardiac failure in the form of hepatomegaly.

Cardiac failure: as a clinical and physical finding, cardiac failure has presented almost exclusively in the form of hepatomegaly (defined as the liver $\geq 1\frac{1}{2}$ finger widths below the costal margin). Rales over the lungs may have been a sign of cardiac failure, but may also be caused by accompanying pneumonia. Hepatomegaly was found very frequently in the material (in 41.9% of the children who were examined before the age of 2 years), and earlier in premature infants than in full-term infants. Cardiac failure is found with increasing frequency with increasing pressure in RV or PA, but without any definite dependence on size of shunt. No edema whatever was demonstrated.

Reduced endurance in feeding does not occur with any great frequency in the present study, presumably because of the great preponderance of quite small infants. The symptom occurs apparently more frequently in the case of large left-to-right shunts than in the case of high pressure in RV or PA (but the figures are small).

Recurrent pulmonary infection occurs in the anamnesis quite frequently in the material of children examined before the age of 2 years (in not quite 30%).

Rapid cardiac action was found in 2 patients as a constant phenomenon, not of the type paroxysmal tachycardia.

Voussure was demonstrated in 35% of the children under the age of 2 years at first examination, rising in frequency with age. The incidence of voussure appears to increase both with increasing pressure in RV or PA and with increasing size of shunt.

Thrill was found in 26% of the children examined before the age of 2 years. It varies with the severity of the disease. It appears to be constantly present in the moderately severe cases of the disease, but is more uncertain in the quite mild cases and very severe cases (in particular Eisenmenger's syndrome). The incidence of thrill increases with increasing age. There does not appear to be any definite correlation to pressure or to size of shunt. On the other hand, it is dependent of the strength of the systolic murmur

(found only with degrees of strength "strong" or more).

The systolic murmur was found in all patients except 3, in whom it was not heard until later than the first cardiological examination. 95% of the children who were examined before the age of 2 years had a "moderately strong" murmur or stronger, while only 5% (7 children) had a weak systolic murmur or no murmur. The typical localization of the maximum of the murmur in practically all the degrees of strength is "at the lower left sternal border", and particularly so the stronger the murmur; the next frequent localization is "diffusely along the left sternal border". More rarely, other localizations appear. The pressure in RV or PA is best correlated with the typical localization of the maximum of the murmur at low pressures; the higher the pressure, the greater the tendency for the murmur to occur at more unusual sites; this does not hold for the correlation with the size of the shunt. Further, it was found that the stronger the systolic murmur, the more the patients treated are distributed uniformly among the various magnitudes of pressure in RV or PA; conversely, the weaker the murmur, the more certain it is that the pressure in RV or PA is high.

A diastolic murmur was found in 12 patients under the age of 2 years at first cardiological examination. In one patient it was heard over the pulmonary ostium. Five patients had an apical diastolic murmur, in all cases rather weak, occurring early in diastole and found in patients with moderately large to large left-to-right shunts. The remaining 6 patients had a short murmur occurring early in diastole and heard along the lower left sternal border.

Anemia was not found strikingly frequently and not more frequently in children with than in children without recurrent respiratory tract infections. The hemoglobin values found do not appear to be correlated in any definite way with the hemodynamic conditions. The "anemia" found is therefore presumably due more to a reduced systemic flow than to a real reduction in the hemoglobin level.

CHAPTER IV

The roentgenological picture of the heart and lungs in isolated VSD in childhood is reviewed, based on the literature (the cardiothoracic index - which is too uncertain a method of measurement and has not been employed in this study - the volume of the heart evaluated from the radiogram of the thorax, including approximate values for maximum normal heart volume in infancy, and the appearance of the pulmonary vessels and aorta). The technique of

recording employed in the present material is reviewed, just as is the calculation of the volume of the heart. The relative volume of the heart is quite well correlated with the pressure in RV or PA, whereas there is no convincing correlation with the size of the left-to-right shunt. On the other hand, the relative volume of the heart is seen to have a certain degree of significance for evaluating the disease isolated VSD: the greater the relative volume, the greater the pressure in RV or PA, and thereby (see the clinical section) the more severe the disease. The material is found to contain only 7 children out of a total of 105 children under the age of 2 years with isolated VSD, who had a normal sized heart (of these only one had pulmonary hypertension). The size of the left atrium and the left ventricle, evaluated from the radiogram of the thorax, is found to be more or less correlated with the magnitude of the pressure in RV or PA and with the size of the left-to-right shunt. The density of the pulmonary vasculature is quite well correlated with the magnitude of the pressure in RV or PA, the size of the left-to-right shunt and the relative volume of the heart. At first examination, strikingly wide central pulmonary vessels and narrow peripheral pulmonary vessels could only be demonstrated with certainty in one case. The magnitude of the region of the pulmonary conus is correlated to some degree with both the magnitude of the pressure in RV or PA and the size of the left-to-right shunt. In the present material, only 5.5% of the cases were found to have a right aortic arch.

CHAPTER V

On the basis of the literature, the ECG in isolated VSD in children is discussed, together with its significance for evaluating the operability of the disease. The ECG records in the present material are referred to, with the norms employed for axis determination and determination of ventricular hypertrophy. The various forms of electric axis in the material of children with isolated VSD under the age of 2 years are found to be as follows: normal axis: 47%, left axis deviation (LAD): 19%, right axis deviation (RAD): 34%. The distribution of ventricular hypertrophy in the same material is as follows: no ventricular hypertrophy: 22%, left ventricular hypertrophy (LVH): 4%, combined ventricular hypertrophy (CVH): 62% and right ventricular hypertrophy (RVH): 12%. The various constellations of electric axis and ventricular hypertrophy are described. If these are examined in relation to the magnitude of the pressure in RV or PA, the size of the left-to-right shunt and the size of the relative volume of the heart, then the lowest valu-

es of pressure, shunt and heart volume are found in those cases where the electric axis is normal and no ventricular hypertrophy is present. Apart from this, the distribution of the various ECG constellations is uniform throughout the various sizes of shunt, although with LAD + CVH occurring more frequently in the case of large left-to-right shunts. With regard to the distribution of the ECG constellations over the various values of pressure in RV or PA, there is a tendency for more of those constellations in which CVH or RVH is included to be found at the high pressures in RV or PA; these last-mentioned ECG constellations have also a tendency to occur more particularly among the slightly enlarged hearts. The amplitude of P_{II} was examined in particular: 34 children out of 124 under the age of 2 years at first examination had an increased P_{II} , and in relation to the pressure in RV or PA, a tendency is found for P_{II} to be increased more frequently than expected in the case of pulmonary hypertension (85% compared to an anticipated 72%). Seven out of the 34 children with an increased P_{II} were found to have elevated pressure in the right atrium. Only one case of incomplete right branch block was found in the material, whereas there were no cases of the other types of branch block and no cases of incomplete or complete a-v block. The value of the ECG for evaluating the relationship between the hemodynamic factors and the electric axis is here of no significance. The ECG is only rarely abnormal in the case of normal or only slightly elevated pressure in RV or PA, and small left-to-right shunts. High pressure in RV or PA most often results in CVH or RVH. Large left-to-right shunts most often result in LAD+CVH.

CHAPTER VI

A brief account is given of the diagnostic value of clinical examination + radiological examination of the thorax + ECG when the patients are examined for the first time. In 93 out of the 144 children (80 out of 124 children under the age of 2 years), the diagnosis of isolated VSD was made solely on the basis of the 3 groups of information mentioned: clinical examination, radiological examination of the thorax, and ECG. It is found that the diagnosis is made with greater certainty, the older the child, and also with greater certainty at low pressures in RV or PA than at high pressures, whereas the size of the shunt does not appear to influence the diagnostic certainty. However, the certainty is not so great that further examination (cardiac catheterization and possibly right-sided angiocardigraphy) is superfluous. Finally, that definitive diagnosis is recorded which was made in the case of 46

children (43 of them under the age of 2 years) after complete examination including catheterization and possibly angiocardiography, and confirmed in some cases by thoracotomy or at autopsy, the original diagnosis of isolated VSD, made on the basis of clinical examination + radiological examination of the thorax + ECG, having been erroneous, either wholly or in part.

CHAPTER VII

After reviewing the literature on cardiac catheterization and right-sided angiocardiography (especially selective angiocardiography), particularly in the younger age groups, the present material is discussed. At first cardiologic examination, a total of 149 catheterizations were performed in 144 children, including 127 of the 124 children under the age of 2 years. The diagnosis of VSD was made by the actual catheterization itself in 11 patients, whose VSD was catheterized directly. The complications which developed from the catheterization are described, being mainly mild and transient, with no deaths. Thereafter follow the normal values used for pressure and oxygen saturation in the material: systolic pressure in RA $\bar{<}$ 6 mmHg, RV: systolic/diastolic pressure $\bar{<}$ 25/4 mmHg, PA: systolic/diastolic pressure $\bar{<}$ 25/10 mmHg. A systolic pressure in RV between 25 and 40 mmHg is considered as a transitional group between normal pressure and pulmonary hypertension, which is defined as a systolic pressure in RV or PA $\bar{>}$ 41 mmHg. The greatest difference in systolic pressure between RV and PA (RV > PA) in the present material is 18 mmHg, which is accepted as being within the normal range according to the literature, especially in patients with large left-to-right shunts, and is explained as being the result of a relative pulmonary stenosis. The minimum difference in oxygen saturation between the caval veins and RA was put at 10% in the present investigation, between RA and RV at 7.5% and between RV and PA at 5%, in order to be significant. (Slightly stricter requirements than in other investigators, because of the restricted number of samples taken in each localization). The diagnosis "isolated VSD" was made - on the basis of the oxygen saturation determinations - if the difference between oxygen saturation in RA and RV (possibly PA) was $\bar{>}$ 7.5%, when at the same time no left-to-right shunt could be demonstrated on the atrial plane, and the diagnosis "persistent ductus arteriosus" or "aortico-pulmonary window" could be shown to be unlikely by catheterization. Only in very few cases has it been possible to obtain oxygen saturation determinations from the arterial blood (and measurements of oxygen uptake through the lungs have not been made in the present study).

Rather few pressure and oxygen saturation measurements have been made in each localization, especially because it was desirable to carry through the investigations as rapidly as possible and draw as little blood as possible in children who were often in very poor condition at the time of the investigation. Pressure in RA was found to be elevated in a total of 18 patients (= 15%), all under the age of 2 years. This increase in pressure was only found in patients with pulmonary hypertension, and in particular in presumed pressure equalization between RV and LV. The rightsided angiocardiograms are then reviewed, almost all of which have been selective (89 selective and 5 venous). The complications encountered on angiocardiography are reviewed. There were no deaths. The diagnosis of isolated VSD is made from angiocardiography in the presence of one or more of the following findings: direct visualization of the defect, signs of recirculation of the contrast in the pulmonary circulation, dilution of contrast on transition from RA to RV, simultaneous filling of both ventricles and/or strong contrast filling of PA/weak contrast filling of aorta on injection into LV. (Several of the findings are often present in the same patient). Strikingly wide central and narrow peripheral pulmonary vessels were only found on angiocardiography in 2 patients, and even then the findings were not convincing. In 10 out of 11 children in whom the VSD was visualized directly on angiocardiography, pulmonary hypertension was found, in 6 of the children there was presumably pressure equalization between the ventricles (pressure in RV $\bar{\geq}$ 61 mmHg). It is concluded that cardiac catheterization and possibly right-sided angiocardiography have been decisive for the diagnosis of isolated VSD and for determining the degree of hemodynamic severity of the disease. Such investigations will therefore continue to be indicated when problems of diagnosis and possibilities of treatment arise in a patient in whom the presence of isolated VSD is suspected.

CHAPTER VIII

Based on the literature, a review is given of the hemodynamic conditions during the first 2 years of life in children with isolated VSD. The author's material is then discussed. In the children under the age of 2 years at first examination, when the magnitude of the pressure is related to the size of the shunt, all those patients with poor clinical condition are found to have a systolic pressure in RV or PA $\bar{\geq}$ 48 mmHg, and by far the majority of them a pressure greater than 60 mmHg (i. e. pressure equalization between RV and LV). The size of the shunts in the patients with a poor clinical con-

dition (who as mentioned all have pulmonary hypertension) is distributed uniformly over the various pressure groups, whereas the shunt sizes are clearly smaller in children with a normal or an insignificantly elevated pressure in RV or PA. The 124 children in the material under the age of 2 years are divided into 4 groups: I-IV, with increasing hemodynamic changes, and group IV (with pressure equalization between RV and LV) is in turn divided into group A with the moderately large and large left-to-right shunts and presumably only moderate pulmonary vascular resistance, and group B, with small left-to-right shunts and presumably high pulmonary vascular resistance. A corresponding grouping was carried out in the case of the 20 children who were over the age of 2 years at first examination (These did not include any children in group IV B). The division of group IV into A and B was found desirable, because group IV B was expected to contain patients who in addition to having a left-to-right shunt also had a right-to-left shunt. 2 patients may have had a right-to-left shunt, but it was not possible to confirm this. The question is discussed as to what pressure magnitude in RV or PA represents the boundary for the pressure equalization between the ventricles. In infants with a very poor clinical condition, this value presumably lies lower than the value usually quoted: 61 mmHg, but on the other hand it may also be higher in older children with a higher pressure in LV.

CHAPTER IX

This chapter contains a data processing from the anamnesis and the clinical and physical findings, together with the information obtained from a radiological examination of the thorax and from the ECG, the aim of the analysis being to examine whether a grouping of specific single items of information for a given patient with isolated VSD could provide such definite information on the magnitude of the pressure and the size of the shunt in this patient, that cardiac catheterization could be avoided. The conclusion of the data processing of the values used is that no values or grouping of values can be found from the anamnesis, the clinical and physical examination, the radiological examination of the thorax and the ECG, which provide sufficiently definite information on the pressure in the RV or the size of the left-to-right shunt in the individual patient, to make cardiac catheterization superfluous.

CHAPTER X

The medical treatment of the patients in the material who were under the age of 2 years at first examination has been divided into digitalis treatment and the other forms of medical treatment. Treatment with digitalis was not carried out beyond a maximum age of 2 3/4 years. The other forms of medical treatment have consisted of treatment with antibiotics, oxygen, opiates, ephedrine and theophyllamine, as well as postural drainage and frequent small meals, possibly given by tube. It appears that digitalis treatment has been employed considerably more frequently in the second half of the period from which the material originates than in the first half; the material has therefore been divided into two groups from 1954-1959 and 1960-1963, respectively. Treatment by means of digitalis alone appears to have signified an improvement in the results of the medical treatment when a comparison is made between the two treatment periods. The same is the case for combined digitalis treatment and other medical treatment. It should be added here that among the patients who were not medically treated are 13 children in the first period and 2 in the second period, who do not appear to have had the chance of treatment in the form of medical therapy which it would seem they should have had. Medical treatment has become increasingly effective in the course of the years, but hardly effective enough during the period covered by the present material.

CHAPTER XI

Based on the studies in the literature, the radical operations in isolated VSD are first mentioned briefly, and then the various forms of palliative operation. The author's material is reviewed: a total of 41 patients out of the 144 children in the material underwent operative treatment, 39 of these children having been examined for the first time before the age of 2 years. Eight patients underwent radical operation, 5 of them shortly after the first cardiologic examination, all of whom died. Three patients were operated on later, one of whom died. Radical operation on children under the age of 2 years was given up in 1957 because of technical difficulties. A palliative operation, consisting of constriction of the pulmonary artery: the Dammann-Müller operation, the Dammann-Müller modified operation and the Dammann-Müller-Albert operation, was performed in 5, 4 and 24 patients, respectively, a total of 33, all under the age of 2 years (with a view to subsequent radical operation); one of these patients underwent radical operation later, but

died. Of the 32 patients who underwent palliative operation, only 18 are alive. Of the 14 patients who died, 12 died as a sequel to the operation, or during the post-operative period. The indications for operation were as follows: pulmonary hypertension (26 of the 33 having pressure equalization between the ventricles) and varyingly great, often very great left-to-right shunt and such a poor general and cardiac condition (inability to thrive, tachypnoea, recurrent pulmonary infections and cardiac failure), that no effective medical treatment was possible. A comparison was made between the group of patients who underwent palliative operation and a group of children who were not operated on, but who were just as severely affected hemodynamically. Anamnesis, physical and clinical findings, ability to thrive in hospital, radiogram of the thorax, ECG, size of left-to-right shunt and magnitude of the pressure in RA were all compared. There are 4 points on which the group of children operated on were found to be in a poorer condition than those not operated on: 1. The incidence of 2-6 of the most important physical and clinical findings is greater in the group of those operated on. 2. The ability to thrive under optimum conditions (in hospital) is poorer in the group of those operated on. 3. The relative volume of the heart is greater in the group operated on, and 4. The signs of left-sided stress on the ECG are more frequent in the group operated on. Even though the 2 groups are hemodynamically comparable as indicated, the group operated on is thus in a poorer condition than the group not operated on. In 29 out of the 33 children operated on, the time of operation lies between the ages of 2 months and 8 months, which is a good indication of the state of the pulmonary arterioles during the period in question. The operative mortality is high in the Dammann-Müller operation (60%) and in the modified Dammann-Müller operation (75%), whereas it is lower (and corresponds to the reports in the literature) in the Dammann-Müller-Albert operation: 25%. The mortality incidence is not correlated with the degree of constriction. The effect of the palliative operation, apart from the first difficult postoperative days, is usually good, with a decrease in tendency to cardiac failure and in respiratory tract symptoms, together with improved ability to thrive.

CHAPTER XII

This chapter provides a quite brief review of the histological findings in the pulmonary vessels in 19 of the dead infants with isolated VSD in the material, and of the significance of a pulmonary biopsy for an evaluation of the operability of the disease "isolated VSD". Operation biopsies from the lingula

pulmonis obtained during the palliative operations are not representative of the vascular histology of the pulmonary tissue as a whole.

CHAPTER XIII

This chapter on the follow-up examination commences with a survey of the present view of the course of the disease "isolated VSD" after the age of infancy, either spontaneously or following palliative operation. After infancy, the spontaneous course may have the following character: 1. A slow improvement in the hemodynamic and thereby the clinical conditions (on account of the persistence of the medial thickening in the pulmonary arterioles and a general adjustment to this state of affairs, a relative reduction in the VSD, a gradual closing - possibly even total - of the VSD or the development of an infundibular pulmonary stenosis). 2. An unchanged, quite satisfactory state up to the 2nd to 3rd decade, at which time there again develops a slow exacerbation of the disease. 3. A progression of the disease on account of rapidly increasing changes in the pulmonary arterioles - in rather a few patients - all the way from infancy up to death during the 1st-2nd decade.

The author's material is then reviewed. Among the surviving patients from the period of investigation 1954 to 1960 (76), all were followed-up with the exception of one, and all those 63 who were under the age of 2 years at the first cardiological examination, including the 15 who underwent palliative operation and who survived the operation. Recatheterizations were performed in 15 cases (9 patients not operated on and 6 who underwent palliative operation). In those who were not operated on, the hemodynamic conditions were found to be unchanged in 3, improved in 4 and exacerbated in one, as well as changed in one on account of the development of an infundibular pulmonary stenosis. Recatheterization of those who underwent palliative operation showed that the operation had been successful in those 5 of the 6 patients where the result could be evaluated.

Clinical picture at follow-up examination: the anamnesitic symptoms: failure to thrive, shortness of breath, tendency to cyanosis, recurrent pulmonary infections, had all decreased since the first examination, both in those not operated on and in those operated on, while reduced endurance occurred more frequently than at first examination. In addition, particularly those who had been operated on had a tendency to cyanosis on effort. Reviewing the change in the incidence of the anamnesitic symptoms from first examination to follow-up examination, it is found that the lower the value

the systolic pressure in RV or PA had been at first examination, the fewer patients who had persistent anamnestic symptoms after the first 2 years of life. In one, the VSD had closed spontaneously. All those children who had undergone palliative operation and who survived the operation improved, but not to the same degree and not with equal rapidity. The clinical improvement was found to be independent of the pressure gradient in the PA obtained as a result of the operation. Those patients who were not operated on and who were over the age of 2 years at first examination also improved in the course of time, and in general the disease ran a milder course. The sole physical finding which definitely decreased up to the time of the follow-up examination was tachypnoea. The increase in weight was found to be clearly dependent on the magnitude of the pressure in RV or PA at first examination; the lower the pressure the more patients who achieved normal weight up to the time of the follow-up examination. In the case of those who underwent palliative operation - all of whom had pulmonary hypertension at first examination - the same tendency held. The change in weight was found to be even more clearly dependent on the magnitude of the pressure in RV or PA at first examination. If the weight in those 15 who were operated on is compared with the weight in those 17 who were not operated on but who had the same hemodynamic conditions, no definite difference is found, but it should be recalled that the clinical condition in those who underwent palliative operation was poorer than in those who were not operated on. Furthermore, it is found that in those with pulmonary hypertension who were not operated on, it is in particular the patients with presumed high pulmonary vascular resistance who continue to thrive poorly. Height improves somewhat by the time of the follow-up examination, but the changes are not great. Five patients at follow-up examination are presumed to have developed an Eisenmenger's syndrome (or possibly Fallot's tetralogy). Vossure - and thrill - are recorded considerably more frequently at follow-up examination. The incidence of vossure increases with increasing pressure in RV or PA (at first examination), but is independent of the size of the shunt; the incidence of thrill appears to be independent of the hemodynamic conditions at first examination. The maximum of the systolic murmur at follow-up examination in those not operated on is generally speaking found to be the same as at first examination. Six patients had a weak murmur; in 3 of them, it is possible that the VSD was about to close, while in the other 3 it is possible that the weak murmur is due to an approximate pressure equalization between the ventricles. Those who underwent palliative operation all had a pronounced systolic murmur at follow-up examination also at the upper left sternal border.

Finally, the neurological or mental disturbances found at follow-up examination are reviewed. Only one case of slight mental retardation had developed, not previously recognized. It is concluded that no causal relationship can be demonstrated between the neurological or mental disturbances in the patients in question and their cardiac disease (apart from the tendency for mongols to develop congenital heart disease).

Radiological picture at follow-up examination: The relative volume of the heart remained enlarged in the majority in the course of time. In the case of the children who were not operated on, it was found that the relative volume of the heart showed a weak falling tendency in all groups of pressure values in RV or PA (at first examination). This tendency also holds for those children examined for the first time after the age of 2 years. In the case of the children who underwent palliative operation, they were all found to show a decreasing relative volume, although this did not become normalized. The pressure gradient in the PA achieved as a result of the palliative operation was not found to be correlated with the size of the heart at follow-up examination. The size of the left atrium and left ventricle was found to be well correlated with the magnitude of the pressure and the size of the shunt (from first examination), and a tendency was found to normalization or at any rate to a decrease in the size of these two chambers of the heart at the time of the follow-up examination, this being greatest in the case of the left atrium; the same held for the density of the pulmonary vasculature and in particular among those who had undergone palliative operation. On the other hand, the pulmonary conus remained almost unchanged from the first examination. Specially narrow peripheral and wide central pulmonary vessels have not been demonstrated with certainty at follow-up examination except in one patient, who had developed a condition of severe pulmonary hypertension (but not in those cases presumed to have developed into Eisenmenger's syndrome).

Electrocardiography on follow-up examination: In the case of the children not operated on - examined for the first time before the age of 2 years - a development has appeared from first examination: The least severe ECG constellations (normal axis or LAD + no ventricular hypertrophy, LVH or CVH) tend towards an improvement and possibly a normalization. The more severe ECG constellations (RAD + CVH and RAD + RVH), on the other hand, appear to have deteriorated from first examination to follow-up examination. In children who have developed Eisenmenger's complex, the ECG as a rule shows a tendency to right axis deviation. In the case of children not operated on - examined for the first time after the age of 2 years - the appearance of the ECG shows a considerable stability. In the

case of the children who had undergone palliative operation, a pronounced tendency to right axis deviation was found in the ECG from before the operation to the time of the follow-up examination (2-7 years after the operation).

CHAPTER XIV

In this chapter, the question is examined whether the aim of the study as indicated in chapter I has been achieved:

1. The disease picture: "isolated VSD in infants", is discussed in detail from the point of view of anamnesis, physical and clinical findings, radiological examination, electrocardiographic examination, and from what is revealed by cardiac catheterization and possibly right-sided angiocardiography, and finally as a result of a follow-up examination of the children.

2. It has been found that the use of a combination of anamnestic data, physical and clinical findings and roentgenological and electrocardiographic results, has by itself been unable to provide so certain a diagnosis and information as to the hemodynamic conditions, that cardiac catheterization and possibly angiocardiography could be regarded as superfluous. However, in spite of this conclusion, it has been found valuable to relate the condition of the children to the hemodynamic findings, as the anamnestic, clinical, radiological and electrocardiographical findings in the children have shown some degree of dependence on the magnitude of the pressure in RV or PA and on the size of the left-to-right shunt, especially the first: the poorer the condition, the more often severe hemodynamic changes are observed. Four points have been found (see chapter XI) which are essential for the decision as to whether intense medical treatment, or possibly palliative operation, is indicated.

3. The palliative operations have been a valuable therapeutic aid in the most severe cases of isolated VSD in children under the age of 6 months, and in the opinion of the author, are still justified in spite of the relatively great mortality, provided that the choice of the patients for operation is made with great care.

Danish Summary

KAPITEL I

Der gives en kort redegørelse for formålet med nærværende arbejde: 1. En gennemgang af sygdomsbilledet "Isoleret ventrikelseptumdefekt" (isol. VSD), som det viser sig hos børn fortrinsvis i aldersgruppen under 2 år. 2. En undersøgelse af om hjertekatheterisation og eventuelt højresidig angiocardiografi kan undværes ved kombination af tilstrækkeligt detaljerede anamnesticke og objektive kliniske oplysninger kombineret med RU af thorax og Ekg; og såfremt dette ikke er tilfældet, da om man ved hjælp af supplerende hjertekatheterisation og eventuelt højresidig angiocardiografi var i stand til at udskille blandt de dårligste patienter en gruppe, der krævede særlig intens medicinsk behandling, eventuelt en palliativ operation. 3. En vurdering af resultaterne af de palliative operationer.

KAPITEL II

Eget materiale består af samtlige hjertekatheterisationsmæssigt verificerede børn med isol. VSD undersøgt på Cardiologisk Laboratorium på Dronning Louises Børnehospital i perioden august 1954 - udgangen af 1963: ialt 144 børn af 853 børn med påvist hjertesygdom, heraf 124 under 2 år på undersøgelsestidspunktet. Af de 97 børn af de 144, som er undersøgt inden udgangen af 1960, er 75 af 76 overlevende efterundersøgt inden udgangen af 1963; de resterende 47 fra undersøgelsesperioden 1961 - 1963 er ikke efterundersøgt. Oplysningerne om de efterundersøgte patienter er ajourført til udgangen af

1963 (med undtagelse af een). Det understreges, at vægten ved gennemgangen af materialet er lagt på aldersgruppen under to år, den aldersperiode i hvilken de største forandringer indtræffer ved isol. VSD. Hyppigheden af isol. VSD blandt congenitte hjertesygdomme i nærværende materiale findes at være 16.9% af samtlige undersøgte børn; 18.1% af børn undersøgt under 2 års alderen. Under gennemgangen af ætiologien angives den familiære disposition i nærværende materiale til 11.3%. Graviditetskomplikationer er fundet hos 11.6% af materialets patienter. Det understreges, at der kun er oplyst eet tilfælde af ikke nærmere karakteriseret infektion i graviditetens første tredjedel, altså ingen sikre tilfælde af rubellainfektion. Moderens og faderens alder afviger ikke i materialet fra alderen i normalbefolkningen, ej heller frekvensen af fødselskomplikationer; derimod er frekvensen af fødselsvægt under 2500 g højere end normalt (17.7% mod normalt varierende mellem 3 og 12%). Fordelingen af børnenes fødselstidspunkt på året viser ingen sæsonophobning. Der er fundet congenitte, ikke-cardiale defekter (inclusive mongolismus) hos 24.3% af patienterne. Materialets køns- og aldersfordeling: der er 83 piger og 61 drenge i totalmaterialet på 144 børn (70 piger og 54 drenge undersøgt før 2 års alderen). Forskellen mellem de to køn er ikke signifikant. Tendensen til overvægt af piger påpeges, da en overvægt af drenge var at vente. Yngste patienter var under 1 måned, ældste 10 år ved første undersøgelse. Spontan mortalitet (d. v. s. ikke kirurgisk betinget) kan ikke udregnes i materialet, da næsten alle de dårligste patienter har været henvist til korrektiv eller palliativ operation. Kun 6 er døde uden operation.

KAPITEL III

Kapitel III er en gennemgang af de anamnesticke og objektive kliniske symptomer sat i relation til størrelsen af det systoliske tryk i RV/PA og til venstre-højre shuntens størrelse udtrykt i forskellen i iltmætningsprocenten mellem RV og RA (idet iltoptagelsen gennem lungerne ikke er målt hos materialets patienter og den arterielle iltmætning kun hos ganske få. Systemflowets størrelse, den vasculære pulmonale resistance og flowratio har derfor ikke kunnet udregnes). Efter en litteraturoversigt over de kliniske symptomer ved isol. VSD gennemgås eget materiale; man har anvendt den arbejdshypothese, at patienternes tilstand især er afhængig af trykket i RV/PA og venstre-højre shuntens størrelse og derfor vurderet de enkelte forhold, der gennemgås, i forhold til disse to parametre. Det første anamnesticke oplyste cardiale symptom forekom hos 138 af de 144 børn før 2 års alderen, hos 120 af de 144 før 6 måneders alderen. Det vises, at sværhedsgraden udtrykt ved størrelsen

af det systoliske tryk i RV/PA eller af venstre-højre shuntten ikke influerer på tidspunktet for erkendelsen af det første anamnesticke symptom. De symptomer, der tidligst fører til cardial undersøgelse, er dårlig trivsel og tachypnoe, hvorimod mislyd som eneste symptom ikke nødvendigvis har ført til tidlig cardial undersøgelse. Henvisningsårsager til undersøgelsen som recidiverende lungeinfektioner (med heraf følgende opdagelse af hjertelidelsen), dårlig trivsel og tachypnoe er ofte korreleret til hæmodynamisk svære tilfælde af isol. VSD, specielt vurderet ud fra størrelsen af trykket i RV/PA.

De 5 vigtigste subjektive symptomer er efter hyppighed: dårlig trivsel, tachypnoe ved anstrengelse, cyanose ved anstrengelse, tachypnoe i ro og recidiverende lungeinfektioner. Der er fundet en tydelig sammenhæng mellem hyppigheden af symptomerne og størrelsen af det systoliske tryk i RV/PA, mens denne korrelation kun er fundet i ringe grad over for shuntstørrelsen. Det viser sig endvidere, at jo flere af de hyppigst forekommende anamnesticke symptomer, der findes hos en patient, jo sværere er sygdommen bedømt ud fra størrelsen af det systoliske tryk i RV/PA og - i mindre grad - ud fra størrelsen af venstre-højre shuntten. Hos patienter med pulmonal hypertension (systolisk tryk i RV/PA ≥ 41 mmHg) respektive en shuntstørrelse - udtrykt i iltmætningsdeficitet RV - RA i % - $\geq 15\%$, finder man 3 af de nævnte 5 symptomer hos over halvdelen af patienterne.

Det hyppigst forekommende objektive symptom er den systoliske mislyd (forekom hos 141 af de 144 patienter). De hyppigste objektive symptomer her efter har efter hyppighed været: dårlig trivsel, tachypnoe ved anstrengelse, tachypnoe i ro, hepatomegali og voussure. Disse 5 symptomer har vist tiltagende hyppighed ved stigende systolisk tryk i RV/PA, mens dette har været meget mindre udtalt ved stigende shuntstørrelse. Jo flere af disse hyppigst forekommende objektive symptomer (bortset fra mislyden), der findes hos en patient, jo alvorligere er sygdommen hæmodynamisk set. Det gælder både når symptomerne sættes i relation til shuntstørrelsen og til størrelsen af det systoliske tryk i RV/PA, men tydeligst i sidste tilfælde. Hos patienter med et systolisk tryk i RV/PA ≥ 61 mmHg finder man 4 af de anførte 5 symptomer hos næsten 3/4 af patienterne, og ved en shuntstørrelse på $\geq 15\%$ (iltmætningsdeficit RV - RA) finder man 4 af de anførte 5 symptomer hos over halvdelen af patienterne.

De enkelte anamnesticke og objektive kliniske symptomer:

Dårlig trivsel som anamnestic symptom findes med stigende hyppighed ved stigende tryk i RV/PA, hvorimod korrelationen til shuntstørrelsen ikke er påfaldende. Man har angivet det forhold, at længde- respektive højdevæksten oftest er mindre hæmmet end vægtøgningen ved et særligt begreb betegnet "dårligt huld" ("dårligt huld" forekommer sjældnere end dårlig trivsel).

Aldersvægtens - og i mindre grad højdevægtens - afhængighed af det systoliske tryk i RV/PA er tydelig: jo større tryk, jo større vægthæmning; derimod synes alders- og højdevægthæmningen ikke sikkert afhængig af shuntstørrelsen. Hvis man hos patienter med trykudligning mellem ventriklerne (i dette arbejde sat til et systolisk tryk i RV/PA $\bar{\geq}$ 61 mmHg) kan gå ud fra, at shuntstørrelsen er omvendt proportional med lungekarresistansen, finder man, at der ikke er nogen sikker korrelation mellem den pulmonale vasculære resistance og størrelsen af vægthæmningen (se imidlertid under efterundersøgelsen, kapitel XIII). Længde- respektive højdevæksthæmningen findes at være noget afhængig af størrelsen af trykket i RV/PA (omend påvirkningen ikke er kraftig), men kun i ringe grad af shuntstørrelsen. Væksthæmningen er i dette materiale ikke fundet afhængig af tilstedeværelsen af recidiverende luftvejsinfektioner.

Tachypnoe i ro og ved anstrengelse er fundet tiltagende ved stigende tryk i RV/PA, men ikke sikkert afhængig af shuntstørrelsen; desuden er tachypnoe'en fundet hyppigere, jo større hjertets relative volumen er.

Cyanose i ro og ved anstrengelse: anamnestisk har perifer og central cyanose ikke kunnet adskilles. Cyanosen kan efter de hæmodynamiske forhold være forårsaget af intermitterende højre-venstre shunt, specielt anstrengelsescyanosen. 16 patienter under 2 år havde anstrengelsescyanose, heraf havde de 15 pulmonal hypertension med mulighed for trykudligning mellem RV og LV. Men dårlig perifer circulation kan tænkes som en anden forklaring på cyanosen. Endelig foreligger der mulighed for, at respirationsvanskeligheder ved hjerteinsufficiens kan være - medvirkende - årsag til cyanosen. 7 af de 13 børn med anstrengelsescyanose, som ikke havde oplysninger om iltmætningen i LA eller i LV, havde tegn på hjerteinsufficiens i form af hepatomegali.

Hjerteinsufficiens: som objektivt symptom har hjerteinsufficiens i langt overvejende grad vist sig i form af hepatomegali (defineret som hepar $\bar{\geq}$ $1\frac{1}{2}$ fingersbredde u. c.). Rallelyde over lungerne kan have været tegn på hjerteinsufficiens, men kan også være forårsaget af ledsagende pneumoni. Hepatomegali er fundet meget hyppigt i materialet (hos 41. 9% af børnene undersøgt før 2 års alderen), og tidligere hos præmature end hos mature børn. Hjerteinsufficiens er fundet med stigende hyppighed ved stigende tryk i RV/PA, men uden sikker afhængighed af shuntstørrelsen. Ødemer er overhovedet ikke påvist.

Nedsat udholdenhed forekommer ikke særligt hyppigt i nærværende arbejde, formentlig på grund af den store overvægt af ganske spæde børn. Symptomet optræder tilsyneladende hyppigere ved store venstre-højre shunter end ved højt tryk i RV/PA (men tallene er små).

Recidiverende lungeinfektioner optræder anamnestisk ret hyppigt i materialet af børn undersøgt før 2 års alderen (hos knapt 30%).

Påskyndet hjerteaktion er fundet hos 2 patienter som konstant fænomen, ikke af typen paroxystisk tachycardi.

Voussure er påvist hos 35% af børnene under 2 år ved den første undersøgelse og stigende i hyppighed med alderen. Hyppigheden synes at stige såvel med stigende tryk i RV/PA som med stigende shuntstørrelse.

Fremissement er fundet hos 26% af børn undersøgt før 2 års alderen. Det varierer med graviteten af sygdommen. Det synes konstant til stede ved de middelsvære tilfælde af sygdommen, mere usikkert ved de ganske lette og meget svære tilfælde (specielt Eisenmengers syndrom). Hyppigheden af fremissement tager til med stigende alder. Det synes ikke sikkert korreleret til tryk - eller shuntstørrelsen. Derimod er det afhængig af styrken af den systoliske mislyd (findes kun ved styrkegraderne "kraftig" eller stærkere).

Den systoliske mislyd er fundet hos alle patienterne undtagen hos 3, hos hvem den først hørtes senere end ved den primære undersøgelse. 95% af børnene undersøgt før 2 års alderen havde en "middelkraftig" mislyd eller kraftigere, kun 5% (7 børn) havde en svag systolisk mislyd eller ingen mislyd. Den typiske lokalisation af mislydens maximum af så at sige alle styrkegrader er: "ved nedre venstre sternalrand", specielt dog jo stærkere mislyden er; næsthypigste lokalisation er: "diffust langs venstre sternalrand". Sjældnere forekommer andre lokalisationer. Trykket i RV/PA er bedst korreleret til den typiske lokalisering af mislydens maximum ved de lave tryk; jo højere tryk jo større tendens er der til, at mislyden optræder på mere usædvanlige steder; dette gælder ikke korrelationen til shuntstørrelsen. Endvidere findes det, at jo kraftigere den systoliske mislyd er, jo mere ligeligt fordeler de omhandlede patienter sig på de forskellige størrelser af tryk i RV/PA; jo svagere mislyden er, jo sikrere er det, at trykket i RV/PA er højt.

Diastolisk mislyd fandtes hos 12 patienter under 2 år ved første cardiale undersøgelse. Hos een hørtes den over pulmonalostiet. 5 havde en apical diastolisk mislyd, i alle tilfælde ret svag, tidligt-diastolisk og fundet hos patienter med middelstore - store venstre-højre shunter. De resterende 6 havde en kort, tidligt-diastolisk mislyd ved nedre venstre sternalrand.

Anæmi er ikke fundet påfaldende hyppigt og ikke hyppigere hos børn med end uden recidiverende respirationsvejsinfektioner. De fundne hæmoglobinværdier synes ikke korreleret på nogen bestemt måde til de hæmodynamiske forhold. Den fundne "anæmi" skyldes derfor formentlig snarere et nedsat systemflow end en reel nedsættelse af hæmoglobinniveau'et.

KAPITEL IV

Der gives først en gennemgang af hjertets og lungebilledets røntgenologiske udseende ved isol. VSD i barnealderen baseret på litteraturen (det cardiothoraciske index der er for usikker en målemetode og ikke er anvendt i arbejdet), hjertets volumen vurderet ud fra RU af thorax (herunder omtrentlige værdier for maximale normale hjertevolumina i barnealderen), lungekarrenes og aortas udseende). Eget materiales optageteknik gennemgås, ligesom udregningen af hjertets volumen. Hjertets relative volumen er ret godt korreleret til trykket i RV/PA, derimod ikke overbevisende til venstre-højre shuntens størrelse. Hjertets relative volumen får derved en vis betydning for vurderingen af sygdommen isol. VSD: jo større relativt volumen jo større tryk i RV/PA og dermed (se det kliniske afsnit) jo sværere sygdom. I materialet findes kun 7 børn af ialt 105 børn under 2 år med isol. VSD at have normal hjertestørrelse (heraf havde kun een pulmonal hypertension). Venstre atrium og venstre ventrikels størrelse, vurderet ud fra RU af thorax, findes nogenlunde korreleret både til størrelsen af trykket i RV/PA og til venstre-højre shuntens størrelse. Lungekartætheden er ganske godt korreleret med hensyn til sværhedsgrad til størrelsen af trykket i RV/PA, venstre-højre shunten og hjertets relative volumen. Påfaldende vide centrale og snævre perifere lungekar er ved første undersøgelse kun påvist sikkert i eet tilfælde. Conus pulmonalis-regionens størrelse er i nogen grad korreleret såvel til størrelsen af trykket i RV/PA som til størrelsen af venstre-højre shunten. I materialet er der fundet 5,5% tilfælde af højresidig arcus aortae.

KAPITEL V

Indledningsvis gennemgås på basis af litteraturoplysninger Ekg ved isol. VSD hos børn, samt dets betydning for vurderingen af operabiliteten af sygdommen. Eget materiales Ekg-optagelser og normerne, der er anvendt i materialet for axe- og ventrikulhypertrofibestemmelsen, anføres. De forskellige former for elektrisk axe i materialet af børn med isol. VSD under 2 år findes at være: nat. axe: 47%, venstresidig axedeviation (LAD): 19%, højresidig axedeviation (RAD): 34%. Fordelingen af ventrikulhypertrofi i samme materiale er følgende: Ingen ventrikulhypertrofi: 22%, venstresidig ventrikulhypertrofi (LVH): 4%, kombineret ventrikulhypertrofi (CVH): 62% og højresidig ventrikulhypertrofi (RVH): 12%. De forskellige konstellationer af elektrisk axe og ventrikulhypertrofi anføres. Sættes de i relation til størrel-

sen af trykket i RV/PA, størrelsen af venstre-højre shunt og størrelsen af hjertets relative volumen findes de laveste værdier af tryk, shunt og hjertevolumen i de tilfælde, hvor den elektriske axe er naturlig og der ikke er nogen ventrikelhypertrofi. Herudover findes fordelingen af de forskellige Ekg-konstellationer jævnt fordelt på de forskellige shuntstørrelser, dog med hyppigere optræden af LAD + CVH ved store venstre-højre shunter. Med hensyn til Ekg-konstellationernes fordeling inden for de forskellige trykstørrelser i RV/PA findes der en tendens til, at de konstellationer, i hvilke der indgår CVH eller RVH, hober sig op ved de høje tryk i RV/PA; disse sidste nævnte Ekg-konstellationer har endvidere en tendens til at optræde specielt blandt de lettere forstørrede hjerter. Størrelsen af P_{II} er undersøgt specielt: 34 børn af 124 under 2 år ved første undersøgelse havde en forstørret P_{II} , og sat i relation til trykket i RV/PA findes der en tendens til, at P_{II} hyppigere end ventet findes forstørret ved pulmonal hypertension (85% mod forventet 72%). 7 af de 34 børn med forstørret P_{II} fandtes at have forhøjet tryk i højre atrium. Kun eet tilfælde af inkomplet højresidigt grenblok er fundet i materialet, derimod ingen tilfælde af de øvrige grenblok-typer og ingen tilfælde af inkomplet eller komplet a-v blok. Ekg's betydning for vurderingen af de hæmodynamiske forhold: axens retning er her uden betydning. Ekg er kun sjældent abnormt ved normalt eller kun let forhøjet tryk i RV/PA og små venstre-højre shunter. Højt tryk i RV/PA giver oftest CVH eller RVH. Store venstre-højre shunter giver oftest LAD+CVH.

KAPITEL VI

Den diagnostiske værdi af kliniske oplysninger + RU af thorax + Ekg i materialet ved første undersøgelse anføres kort. 93 af 144 børn (80 af 124 børn under 2 år) fik stillet diagnosen isol. VSD alene på basis af de 3 nævnte oplysningsgrupper: klinik, RU af thorax og Ekg. Det findes, at diagnosen stilles jo sikrere, jo ældre barnet er, endvidere sikrere ved lavt tryk i RV/PA end ved højt tryk, hvorimod shuntstørrelsen ikke synes at influere på den diagnostiske sikkerhed. Men sikkerheden er dog ikke så stor, at yderligere undersøgelse (hjertekatheterisation og eventuelt højresidigt angiografi) er overflødig. Endelig anføres, hvilken endelig diagnose der blev stillet efter fuldstændig undersøgelse inklusive katheterisation og eventuelt angiografi og eventuelt thoracotomi/autopsi hos 46 børn (heraf 43 under 2 års alderen), som primært på basis af klinik + RU af thorax + Ekg havde fået stillet diagnosen isol. VSD (som altså ikke var korrekt).

Efter en litteraturoversigt over hjertekatheterisation og højresidig angiocardio-
diografi (især selektiv) specielt i de yngre aldersgrupper, gennemgås eget
materiale. Der er ved den primære cardiale undersøgelse foretaget ialt
149 katheterisationer på 144 børn, heraf 127 på de 124 børn under 2 år. Diag-
nosen VSD er stillet ved selve katheteriseringen hos 11, hvis VSD direkte er
blevet katheteriseret. Der beskrives de - fortrinsvis lette og kortvarige -
komplikationer, der er optrådt ved katheterisationerne. Der har ingen døds-
fald været. Derefter anføres de anvendte normalværdier for tryk og iltmæt-
ning i materialet: systolisk tryk i RA: $\bar{\leq} 6$ mmHg, RV: systolisk/diastolisk
tryk $\bar{\leq} 25/4$ mmHg, PA: systolisk/diastolisk tryk $\bar{\leq} 25/10$ mmHg. Systolisk
tryk i RV mellem 25 og 40 mmHg er betragtet som en overgangsgruppe mel-
lem normal tension og pulmonal hypertension, der er defineret som systolisk
tryk i RV/PA $\bar{\geq} 41$ mmHg. Den største forskel i systolisk tryk mellem RV
og PA (RV > PA) er i materialet 18 mmHg, hvilket efter litteraturen accepte-
res som værende inden for normalområdet, specielt hos patienter med store
venstre-højre shunter, og forklares som værende forårsaget af en relativ
pulmonalstenose. Minimumsforskellen i iltmætning mellem vv. cavae og RA
er ved undersøgelserne sat til 10%, mellem RA og RV til 7.5% og mellem
RV og PA til 5% for at være signifikant. (Lidt strengere krav end hos andre
undersøgere på grund af det ringe antal prøver, der er taget i hver lokalisa-
tion). Diagnosen isol. VSD er stillet - ud fra iltmætningsbestemmelserne -
hvis forskellen mellem iltmætningen i RA og RV (eventuelt PA) var $\bar{\geq} 7.5\%$,
når der samtidig ikke kunne påvises nogen venstre-højre shunt på atrieplan,
og diagnosen ductus arteriosus persistens eller aortcopulmonalt vindue ved
katheterisation kunne usandsynliggøres. Det har kun i meget få tilfælde væ-
ret muligt at få iltmætningsbestemmelser fra det arterielle blod (og måling
af iltoptagelser gennem lungerne er ikke foretaget i nærværende arbejde).
Der er foretaget ret få tryk- og iltmætningsmålinger i hver lokalisation,
specielt fordi man har ønsket at gennemføre undersøgelserne så hurtigt som
muligt og udtage så lidt blod som muligt hos de ved undersøgelsen ofte me-
get dårlige børn. Trykket i RA er fundet forhøjet hos ialt 18 patienter
(=15%), alle under 2 års alderen. Denne trykforøgelse er kun fundet hos pa-
tienter med pulmonal hypertension og specielt ved formodet trykkudligning
mellem RV og LV. Herefter gennemgås de højresidige angiocardio-
grafier, der næsten alle har været selektive (89 selektive og 5 venøse). Komplika-
tionerne ved angiocardio-
grafierne gennemgås. Der har ingen dødsfald væ-
ret. Diagnosen isol. VSD er angiocardio-
grafisk stillet ved et eller flere
af følgende fund: direkte visualisering af defekten, tegn på recirculation

af kontrasten i lungekredsløbet, fortynding af kontrasten ved overgang fra RA til RV, samtidig fyldning af begge ventrikler og/eller stærk kontrastfyldning af PA/svag kontrastfyldning af aorta ved injektion i LV (Ofte er flere fund gjort hos samme patient). Påfaldende vide centrale og snævre perifere lungekar er ved angiocardiografi kun fundet hos 2 patienter og endda ikke overbevisende. Hos 10 af de 11 børn, hvis VSD direkte visualiseredes ved angiocardiografi, er der fundet pulmonal hypertension, hos 6 af dem formodentlig trykudligning mellem ventriklerne (tryk i RV $\bar{\geq}$ 61 mmHg). Det konkluderes, at hjertekatheterisation og eventuelt højresidig angiocardiografi har været afgørende for diagnosen isol. VSD og for bestemmelsen af sygdommens hæmodynamiske sværhedsgrad og fortsat derfor må være indiceret, når der opstår problemer vedrørende diagnosen og behandlingsmulighederne hos en patient, mistænkt for at have en isol. VSD.

KAPITEL VIII

Indledningsvis gives en på litteraturstudier baseret oversigt over de hæmodynamiske forhold i de første 2 leveår hos børn med isol. VSD. Eget materiale gennemgås herefter. Når trykstørrelsen hos materialets børn under 2 år ved første undersøgelse sættes i relation til shuntstørrelsen, findes alle de klinisk dårlige patienter at have et systolisk tryk i RV/PA $\bar{\geq}$ 48 mmHg, og langt de fleste over 60 mmHg (d. v. s. trykudligning mellem RV og LV). Shuntstørrelserne hos de dårlige patienter (der som anført alle har pulmonal hypertension) fordeler sig jævnt på de forskellige trykgrupper, hvorimod shuntstørrelserne er tydeligt mindre hos børnene med normalt eller ubetydeligt forhøjet tryk i RV/PA. Materialets 124 børn under 2 år inddeles i 4 grupper: I-IV, med stigende hæmodynamiske forandringer, og gruppe IV (med trykudligning mellem RV og LV) deles igen i gruppe A med de middelstore og store venstre-højre shunter og formentlig kun moderat pulmonal vasculær resistance og gruppe B med små venstre-højre shunter og formentlig stor pulmonal vasculær resistance. En tilsvarende inddeling er foretaget af de 20 børn, som ved første undersøgelse var over 2 år. (Her fandtes ingen børn i gruppe IV B). Man har ønsket at opdele gruppe IV i A og B, idet man i gruppe IV B måtte forvente at finde patienterne, der foruden en venstre-højre shunt også havde en højre-venstre shunt. 2 patienter kan have haft en højre-venstre shunt, men det har ikke kunnet bevises. Beliggenheden af den trykstørrelse i RV/PA, der angiver grænsen for trykudligning mellem ventriklerne, diskuteres. Den kan formentlig hos meget dårlige spæde børn ligge lavere end den sædvanligt anførte vær-

di: 61 mmHg, men til gengæld også højere hos ældre børn med højere tryk i LV.

KAPITEL IX

Dette kapitel indeholder databehandling af de anamnesticke og objektive kliniske oplysninger, oplysninger fra RU af thorax og Ekg foretaget med det formål at undersøge, om en sammenstilling af bestemte enkeltoplysninger om en given patient med en isol. VSD var i stand til at give så sikre oplysninger om tryk- og shuntstørrelsen hos denne patient, at hjertekatheterisation kunne undværes. Konklusionen af databehandlingen af de anvendte værdier er, at der ikke kan findes nogen værdier eller sammenstilling af værdier fra anamnese, klinik, RU af thorax og Ekg, der giver tilstrækkeligt sikre oplysninger om størrelsen af trykket i RV/størrelsen af venstre-højre shunt hos den enkelte patient til at overflødiggøre hjertekatheterisation.

KAPITEL X

Den medicinske behandling af materialets patienter, der ved første undersøgelse var under 2 år, er opdelt i digitalisbehandlingen og den øvrige medicinske behandling. Digitalisbehandlingen er ikke gennemført længere end maksimalt til 2 3/4 års alderen. Den øvrige medicinske behandling har bestået i behandling med antibiotica, ilt, morfina, efedrin og theophyllamin, samt stillingsdrainage og hyppige små måltider, eventuelt indgivet per sonde. Da det har vist sig, at digitalisbehandlingen har været anvendt betydeligt hyppigere i den sidste del af den periode, hvorfra materialet stammer end i den første del, har man opdelt materialet i 2 grupper: fra henholdsvis årene 1954-1959 og 1960-1963. Digitalisbehandlingen alene synes at have betydet en bedring i det medicinske behandlingsresultat ved sammenligning mellem de to behandlingsperioder. Det samme gælder for den kombinerede digitalisbehandling og anden medicinsk behandling. Det skal her anføres, at der iblandt de medicinsk ubehandlede patienter er 13 børn i den første periode og 2 i den anden periode, som ikke har fået den chance i form af en medicinsk behandling, som de efter alt at dømme burde have haft. Den medicinske behandling er blevet tiltagende effektiv i årenes løb, men næppe tilstrækkeligt effektiv i den i dette materiale omhandlede periode.

KAPITEL XI

På grundlag af litteraturstudier gennemgås først kort radikaloperationerne ved lsd. VSD, derefter de forskellige former for palliative operationer. Derpå gennemgås eget materiale: 41 patienter ialt af materialets 144 børn er blevet operativt behandlet, heraf har de 39 været undersøgt første gang før 2 års alderen. 8 patienter er radikalopereret, heraf 5 kort efter den primære cardiale undersøgelse - alle døde. 3 er opereret senere, heraf er een død. Radikaloperation af børn under 2 år opgaves 1957 på grund af tekniske vanskeligheder. Palliative, pulmonalisforsnævrende operationer: Dammann-Müllers operation, Dammann-Müllers modificerede operation og Dammann-Müller-Alberts operation er udført på henholdsvis 5, 4 og 24 patienter, ialt 33, alle under 2 år (med senere radikaloperation for øje); heraf er een senere radikalopereret, men død. Af de 32 udelukkende palliativt opererede lever 18. Af de 14 døde, er 12 døde i tilslutning til operationen eller i den postoperative periode. Operationsindikationen har været: patienter med pulmonal hypertension (hos 26 af de 33 med trykudligning mellem ventriklerne) og vekselende stor, ofte meget stor venstre-højre anast og så medtaget almentilstand og cardial tilstand (dårlig trivsel, tachypnoe, recidiverende lungeinfektioner og hjertheinsufficiens), at de ikke har kunnet behandles effektivt medicinsk. Man har sammenlignet den palliativt opererede gruppe patienter med en hæmodynamisk lige så svært påvirket, ikke opereret, gruppe børn. De er sammenlignet med hensyn til anamnese, objektive kliniske symptomer, trivslen på hospitalet, RU af thorax, Ekg, venstre-højre shuntens størrelse og størrelsen af trykket i R.A. Den opererede gruppe børn viser sig på 4 punkter at være dårligere end den ikke opererede: 1. Hyppigheden af 2-6 af de vigtigste objektive, kliniske symptomer er størst i den opererede gruppe. 2. Trivslen under optimale forhold (på hospital) er dårligere i den opererede gruppe. 3. Hjertets relative volumen er større i den opererede gruppe, og 4. Tegne- ne på venstresidigt stress på Ekg er hyppigere i den opererede gruppe. Selvom de 2 grupper som anført er hæmodynamisk sammenlignelige, er den opererede altså dårligere end den ikke-opererede gruppe. Operations- tidspunktet ligger for 29 af de 33 opererede børns vedkommende mellem 2 og 8 måneders alderen, hvilket svarer godt til lungearteriolernes tilstand i den pågældende periode. Operationsmortaliteten er høj ved Dammann-Müllers operation (60%) og den modificerede Dammann-Müllers operation (75%), hvorimod den er lavere (og svarende til litteraturens angivelser) ved Dammann-Müller-Alberts operation: 25%. Mortalitetens størrelse er ikke korreleret til forenævringsgradens størrelse. Effekten af den pallia-

tive operation er - bortset fra de første vanskelige, postoperative døgn - som regel god, med en aftagen af hjerteinsufficienstendensen og respirationsvejssymptomerne og en bedring i trivslen.

KAPITEL XII

Der gives i dette kapitel en ganske kort oversigt over de lungekarhistologiske fund hos 19 af materialets døde børn med isol. VSD, og over lungebiopsiens betydning for vurderingen af operabiliteten af lidelsen isol. VSD: Lingulabiopsier taget under de palliative operationer er ikke repræsentative for lungevævets karhistologi som helhed.

KAPITEL XIII

Dette kapitel om efterundersøgelsen indledes med en gennemgang af den nuværende opfattelse af forløbet af sygdommen isol. VSD efter spædealderen, dels spontant, dels efter palliative operationer. Efter spædealderen kan forløbet spontant have følgende karakter: 1. En langsom bedring af de hæmodynamiske, og dermed kliniske, forhold (på grund af bevarelsen af mediafortykkelsen i lungearteriolerne og en almindelig tilpasning til denne tilstand, en relativ formindskelse af VSD, en gradvis tillukning - eventuelt total - af VSD eller en udvikling af en infundibulær pulmonalstenose). 2. En uforandret ganske god tilstand indtil 2'-3'decade, hvor der så atter kommer en langsom forværring af sygdommen. 3. En progression af sygdommen på grund af hastigt tiltagende forandringer i lungearteriolerne - hos ret få patienter - lige fra spædealderen indtil mors i 1'-2' decade.

Eget materiale gennemgås herefter. Af de overlevende fra undersøgelsesperioden 1954 til 1960 (76) er efterundersøgt alle pånær een, og alle de 63, som var under 2 år ved første cardiale undersøgelse, heriblandt de 15 palliativt opererede, som overlevede operationen. Rekatheterisationer er foretaget i 15 tilfælde (9 ikke-opererede og 6 palliativt opererede). Hos de uopererede fandtes de hæmodynamiske forhold uforandrede hos 3, bedrede hos 4 og forværret hos een, samt ændret hos een på grund af udvikling af en infundibulær pulmonalstenose. Rekatheterisation af de palliativt opererede viste, at operationen havde været vellykket hos de 5 af de 6, hvor resultatet kunne vurderes.

Klinik ved efterundersøgelsen: de subjektive symptomer: dårlig trivsel, kortåndethed, cyanosetendens og recidiverende lungeinfektioner var alle

aftaget siden den første undersøgelse såvel hos de uopererede som hos de opererede, mens nedsat udholdenhed optrådte hyppigere end ved første undersøgelse. Derudover havde specielt de opererede tendens til anstrengelsescyanose. Gennemgås ændringen i hyppigheden af de subjektive symptomer fra første undersøgelse til efterundersøgelsen, findes det, at jo lavere det systoliske tryk i RV/PA havde været ved første undersøgelse, jo færre havde persisterende subjektive symptomer efter de første 2 leveår. Hos een var VSD lukket spontant. De palliativt opererede børn, der overlevede operationen, bedredes alle, men ikke lige udtalt og ikke lige hurtigt. Den kliniske bedring fandtes uafhængig af den ved operationen opnåede trykgradient i PA. De uopererede patienter over 2 år ved første undersøgelse bedredes også med årene, men havde alt i alt et mildere forløb af deres sygdom. Det eneste objektive symptom, som sikkert aftog til efterundersøgelsen, var tachypnoe. Vægtøgningen viste sig tydeligt afhængig af størrelsen af trykket i RV/PA ved første undersøgelse: jo lavere tryk jo flere patienter fik normal vægt til efterundersøgelsen. For de palliativt opererede - der alle havde pulmonal hypertension ved første undersøgelse - gjaldt samme tendens. Vægtændringen viste endnu tydeligere afhængigheden af størrelsen af trykket i RV/PA ved første undersøgelse. Sammenlignes vægten hos de 15 opererede med 17 uopererede med samme hæmodynamiske forhold, findes ingen sikker forskel, men det bør erindres, at de palliativt opererede klinisk var dårligere end de uopererede. Det findes endvidere blandt de uopererede med pulmonal hypertension, at det specielt er patienterne med formodet stor pulmonal vasculær resistance, som vedblivende trives dårligt. Højden bedres noget til efterundersøgelsen, men forandringerne er ikke store. 5 patienter formodes ved efterundersøgelsen at have udviklet et Eisenmengers syndrom (eller eventuelt en Mb. Fallot). Voussure - og fremissement - er registreret betydeligt hyppigere ved efterundersøgelsen; voussurefrekvensen stigende med stigende tryk i RV/PA (ved første undersøgelse), men uafhængig af shuntstørrelsen; fremissementfrekvensen synes uafhængig af de ved første undersøgelse fundne hæmodynamiske forhold. Den systoliske mislyds maximum ved efterundersøgelsen hos de uopererede fandtes stort set som ved første undersøgelse. 6 havde svage mislyde; hos 3 af disse kan VSD være ved at lukke, hos de 3 andre kan den svage mislyd skyldes omtrentlig trykudligning mellem ventriklerne. De palliativt opererede havde alle en kraftig systolisk mislyd ved efterundersøgelsen også opadtil ved venstre sternalrand.

Til slut gennemgås de neurologiske/psykiske lidelser ved efterundersøgelsen: kun een, ikke tidligere erkendt, let mental retardering var kommet til. Det konkluderes, at der ikke kan påvises nogen causal sammenhæng

mellem de pågældende patienters neurologiske/psykiske lidelse og deres cardiale sygdom (bortset fra mongolernes tendens til at få mb. cordis congenitus).

Røntgenologi ved efterundersøgelsen: Hjertets relative volumen holdt sig forstørret hos de fleste med årene. For de uopererede børn fandtes det, at det relative volumen viste en svagt faldende tendens i alle grupperne af trykstørrelser i RV/PA (ved første undersøgelse). Denne tendens gælder også for børnene undersøgt første gang efter 2 års alderen. For de palliativt opererede børns vedkommende fandtes det, at de alle viste et aftagende relativt volumen, uden at det dog normaliseredes. Den ved den palliative operation opnåede trykgradient i PA fandtes ikke korreleret til hjertets størrelse ved efterundersøgelsen. Størrelsen af venstre atrium og ventrikel er fundet godt korreleret til tryk- og shuntstørrelsen (fra første undersøgelse), og der er fundet en tendens til normalisering eller i hvert fald aftagen i størrelsen af de to kamre til efterundersøgelsen, størst for venstre atriums vedkommende; det samme gjaldt lungekartætheden og specielt hos de palliativt opererede. Conus pulmonalis er derimod nærmest uændret fra første undersøgelse. Særligt snævre perifere + vide centrale lungekar er ikke sikkert påvist ved efterundersøgelsen undtagen hos een, der havde udviklet en svær pulmonal hypertension (men ikke i de tilfælde, der formodes at være udviklet til Eisenmengers syndrom).

Elektrocardiografi ved efterundersøgelsen: for de uopererede børns vedkommende - undersøgt første gang før 2 års alderen - er der sket en udvikling fra første undersøgelse: De mindst svære Ekg-konstellationer (nat. axe eller LAD + ingen ventrikelhypertrofi, LVH eller CVH) tenderer mod en bedring eventuelt normalisering. De sværere Ekg-konstellationer (RAD + CVH og RAD + RVH) synes derimod at forværres fra første undersøgelse til efterundersøgelsen. Hos børnene, der har udviklet et Eisenmengers kompleks er Ekg's tendens til højreprægning reglen. Uopererede børn - undersøgt første gang efter 2 års alderen - viser en betydelig stabilitet i Ekg's udseende. For de palliativt opererede børns vedkommende er der fundet en tydelig højreprægning af Ekg fra før operationen til efterundersøgelsen (2-7 år efter operationen).

KAPITEL XIV

I dette kapitel gøres det op, om formålet med arbejdet - angivet i kapitel I - er nået;

1. Sygdomsbilledet: isol. VSD hos små børn er gennemgået detaljeret anma-

nestisk, objektivt, klinisk, røntgenologisk, elektrokardiografisk samt med hjertekatheterisation og eventuelt højresidig angiocardiografi, og endelig gennem en efterundersøgelse af børnene.

2. Anvendelsen af kombinationen af anamnestiske og objektive kliniske, røntgenologiske og elektrokardiografiske oplysninger har ikke alene kunnet give så sikker en diagnose og oplysninger om hæmodynamik, at hjertekatheterisation og eventuelt angiocardiografi har kunnet overflødiggøres. Men man har trods dette fundet det værdifuldt at sætte børnenes tilstand i relation til de hæmodynamiske fund, idet børnenes anamnestiske symptomer, kliniske, røntgenologiske og elektrokardiografiske fund har vist en vis afhængighed af størrelsen af trykket i RV/PA og størrelsen af venstre-højre shunten, specielt det første: jo dårligere tilstand, jo oftere svære hæmodynamiske forandringer. Man har fundet 4 punkter (se kapitel XI) væsentlige for afgørelsen af om særlig intens medicinsk behandling, eventuelt palliativ operation måtte være indiceret.

3. De palliative operationer har været et værdifuldt therapeuticum ved de allersværeste tilfælde af isol. VSD hos børn under $\frac{1}{2}$ år, og har efter forfatterens opfattelse stadig sin berettigelse, trods den relativt store mortalitet, når udvælgelsen af patienterne til operation foretages meget omhyggeligt.

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Abbreviations

ASD	= atrial septal defect
AVC	= atrioventricularis communis
CNS	= central nervous system
c-th-index	= cardiothoracic index
CVH	= combined ventricular hypertrophy
DM	= Dammann-Müller
DMA	= Dammann-Müller-Albert
EEG	= electroencephalography or electroencephalogram
ECG	= electrocardiography or electrocardiogram
Erythr.	= erythrocytes
FO	= foramen ovale
Hg	= mercury
isol. VSD	= isolated ventricular septal defect
LA	= left atrium
LAD	= left axis deviation
LV	= left ventricle
LVH	= left ventricular hypertrophy
PA	= pulmonary artery
PDA	= persistent ductus arteriosus
PEG	= pneumoencephalography
PFO	= persistent foramen ovale
PS	= pulmonary stenosis
PCV	= pulmonary capillary venous pressure
RA	= right atrium
RAD	= right axis deviation
RV	= right ventricle
RVH	= right ventricular hypertrophy
VSD	= ventricular septal defect
DLB	= the Queen Louise's Children's Hospital

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